367 412

STIC-EIC1600/2900

From: STIC-EIC1600/2900@uspto.gov
Sent: Monday, June 27, 2011 3:51 PM
To: Borl, Ibrahim
Cc: STIC-EIC1600/2900
Subject: Confirmation Receipt: 1600 Search Request - 10/598,736

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Requester ----------

Name: **BORL, IBRAHIM D**
Organization: **TC 1600**
Art Unit: **1629**
Employee Number:
Office Location: **REM-4D79**
Phone Number: **(571)270-7020**
Email: **ibrahim.borl@uspto.gov**

Request Detail ----------

Attachment: 10598736.pdf

Case/Application number: **10/598,736** PALM
Priority App. Filing Date: **4/04/2004**
Format for Search Results: **SCORE & EMAIL**

Meaning of unusual acronyms or initialisms:

Identify the novelty:
Method of treating hepatic fibrosis using attached compounds. The class of the compounds is CB1 receptor antagonist.

Additional Comments:
Please further limit the structure search with text search using the concepts described above.

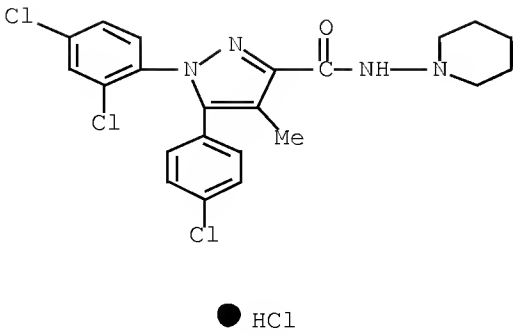
INVENTOR SEARCH

=> d ibib abs hitstr l9 1-4

L9 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2006:537042 HCAPLUS Full-text
DOCUMENT NUMBER: 145:76579
TITLE: CB1 cannabinoid receptor antagonism: a new strategy for the treatment of liver fibrosis
AUTHOR(S): Teixeira-Clerc, Fatima; Julien, Boris; Grenard, Pascale; Van Nhieu, Jeanne Tran; Deveaux, Vanessa; Li, Liying; Serriere-Lanneau, Valerie; Ledent, Catherine; Mallat, Ariane; Lotersztajn, Sophie
CORPORATE SOURCE: INSERM, Unite 581, Hopital Henri Mondor, Creteil, F-9400, Fr.
SOURCE: Nature Medicine (New York, NY, United States) (2006), 12(6), 671-676
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hepatic fibrosis, the common response associated with chronic liver diseases, ultimately leads to cirrhosis, a major public health problem worldwide. We recently showed that activation of hepatic cannabinoid CB2 receptors limits progression of exptl. liver fibrosis. We also found that during the course of chronic hepatitis C, daily cannabis use is an independent predictor of fibrosis progression. Overall, these results suggest that endocannabinoids may drive both CB2-mediated antifibrogenic effects and CB2-independent profibrogenic effects. Here we investigated whether activation of cannabinoid CB1 receptors (encoded by Cnr1) promotes progression of fibrosis. CB1 receptors were highly induced in human cirrhotic samples and in liver fibrogenic cells. Treatment with the CB1 receptor antagonist SR141716A decreased the wound-healing response to acute liver injury and inhibited progression of fibrosis in three models of chronic liver injury. We saw similar changes in Cnr1-/- mice as compared to wild-type mice. Genetic or pharmacol. inactivation of CB1 receptors decreased fibrogenesis by lowering hepatic transforming growth factor (TGF)-β1 and reducing accumulation of fibrogenic cells in the liver after apoptosis and growth inhibition of hepatic myofibroblasts. In conclusion, our study shows that CB1 receptor antagonists hold promise for the treatment of liver fibrosis.

IT 158681-13-1, SR141716A
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(role of CB1 cannabinoid receptor in liver fibrosis and new strategy for treatment)
RN 158681-13-1 HCAPLUS
CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-, hydrochloride (1:1) (CA INDEX NAME)



OS.CITING REF COUNT: 152 THERE ARE 152 CAPLUS RECORDS THAT CITE THIS RECORD (152 CITINGS)
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2005:998698 HCAPLUS Full-text
DOCUMENT NUMBER: 143:279416
TITLE: Antagonists of the CB1 cannabinoid receptor for the treatment of fibrotic diseases of the liver
INVENTOR(S): Lotersztajn, Sophie; Mallat, Ariane ; Grenard, Pascale; Julien, Boris; Nhieu, Jeanne Tran Van
PATENT ASSIGNEE(S): Institut National de la Sante et de la Recherche Medicale INSERM, Fr.
SOURCE: Eur. Pat. Appl., 25 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1574211	A1	20050914	EP 2004-290633	20040309
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK				
AU 2005218937	A1	20050915	AU 2005-218937	20050308
CA 2557976	A1	20050915	CA 2005-2557976	20050308
WO 2005084652	A2	20050915	WO 2005-EP3285	20050308
WO 2005084652	A3	20051208		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1725223	A2	20061129	EP 2005-733278	20050308
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				

CN 1929828	A	20070314	CN 2005-80007516		20050308
BR 2005008560	A	20070814	BR 2005-8560		20050308
JP 2007527893	T	20071004	JP 2007-502312		20050308
RU 2402328	C2	20101027	RU 2006-134707		20050308
EP 2305220	A2	20110406	EP 2010-12234		20050308
EP 2305220	A3	20110518			
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR					
AR 48087	A1	20060329	AR 2005-100905		20050309
ZA 2006007159	A	20080227	ZA 2006-7159		20060828
MX 2006010287	A	20070214	MX 2006-10287		20060908
IN 2006MN01194	A	20070608	IN 2006-MN1194		20061006
NO 2006004603	A	20061009	NO 2006-4603		20061009
US 20080214449	A1	20080904	US 2007-598736		20070719
PRIORITY APPLN. INFO.:			EP 2004-290633	A	20040309
			EP 2005-733278	A3	20050308
			WO 2005-EP3285	W	20050308

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

AB The invention relates to the use of antagonists to the CB1 cannabinoid receptor for the preparation of a composition for the treatment of hepatic diseases and preferably to the use of Rimonabant (N-piperidino-5-(4-chlorophenyl)-1-(2, 4-dichloropenyl)-4-methylpyrazole-3-carboxamide). The mRNA for the CB1 receptor is more abundant in cirrhotic liver than in healthy liver. Mice lacking the CB1 receptor are more resistant to fibrotic change in the liver.

IT 864199-39-3D, substitution variants 864199-40-6D, substitution variants
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence, antagonists for; antagonists of CB1 cannabinoid receptor for treatment of fibrotic diseases of liver)

RN 864199-39-3 HCAPLUS

CN Cannabinoid receptor, type CB1 (human clone EP1574211-SEQID-1) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 864199-40-6 HCAPLUS

CN Cannabinoid receptor, type CB1 (human clone EP1574211-SEQID-2) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

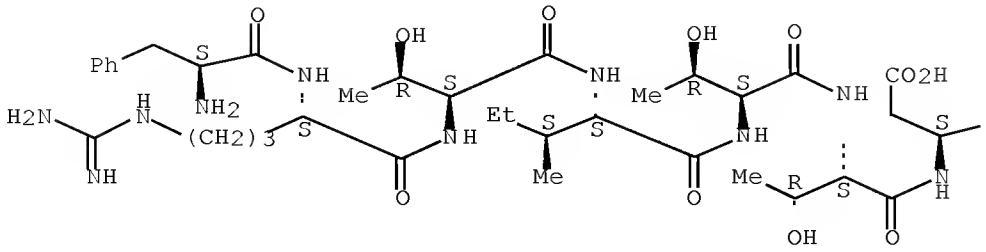
IT 864169-03-9 864169-06-2 864169-08-4
864169-10-8 864169-12-0 864169-16-4
864169-17-5
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence, fragment of CB1 cannabinoid receptor; antagonists of CB1 cannabinoid receptor for treatment of fibrotic diseases of liver)

RN 864169-03-9 HCAPLUS

CN L-Aspartic acid, L-phenylalanyl-L-arginyl-L-threonyl-L-isoleucyl-L-threonyl-L-threonyl-L-α-aspartyl-L-leucyl-L-leucyl-L-tyrosyl-L-valylglycyl-L-seryl-L-asparaginyl-L-α-aspartyl-L-isoleucyl-L-glutaminyl-L-tyrosyl-L-α-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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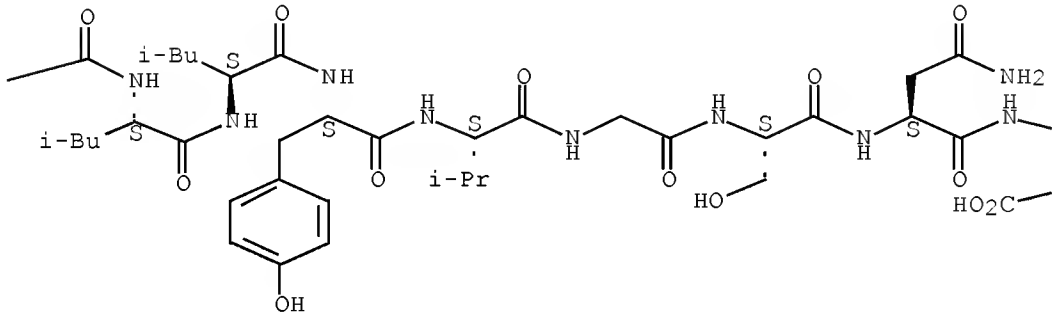

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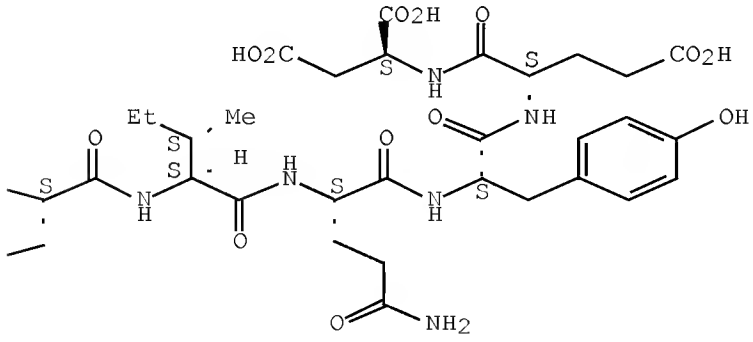

RN 864169-06-2 HCAPLUS

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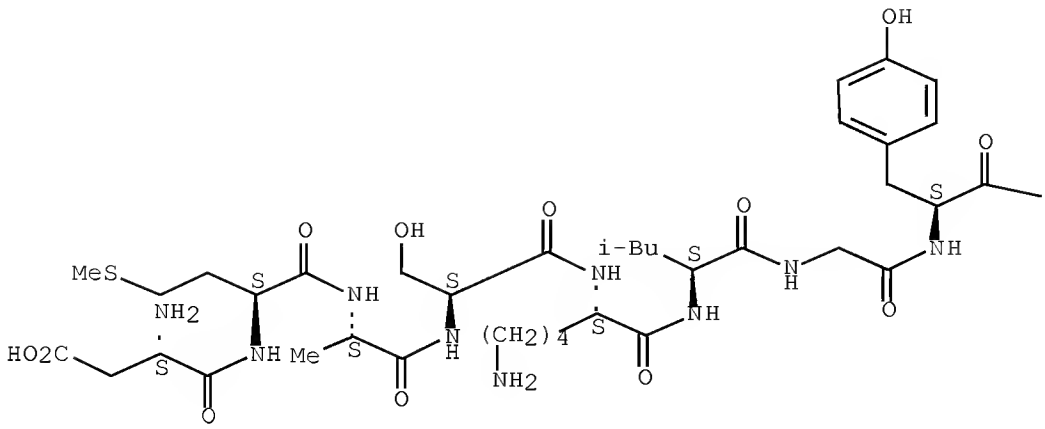
Absolute stereochemistry.

PAGE 1-A



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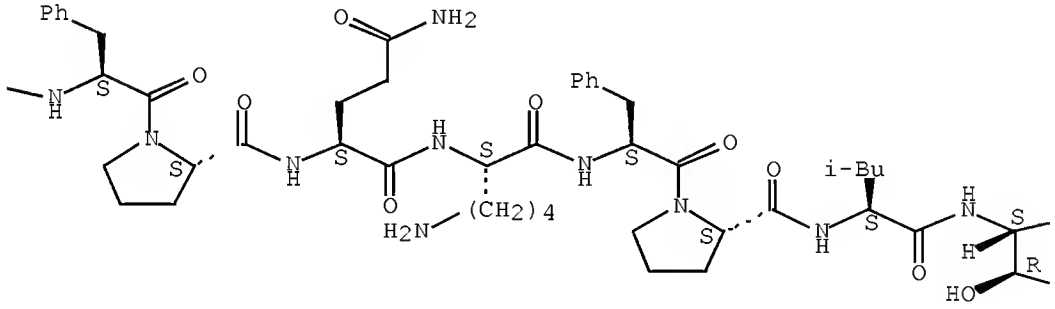

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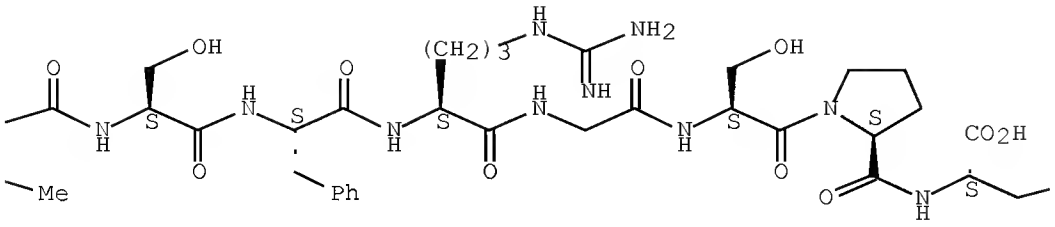


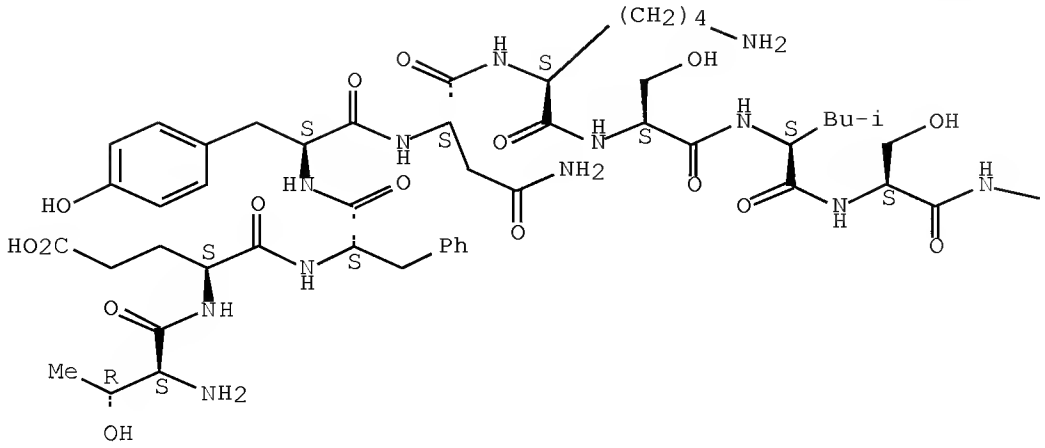
PAGE 1-D

RN 864169-08-4 HCAPLUS

CN L-Cysteine, L-threonyl-L-α-glutamyl-L-phenylalanyl-L-tyrosyl-L-asparaginyl-L-lysyl-L-seryl-L-leucyl-L-seryl-L-seryl-L-phenylalanyl-L-lysyl-L-α-glutamyl-L-asparaginyl-L-α-glutamyl-L-α-glutamyl-L-asparaginyl-L-isoleucyl-L-glutaminyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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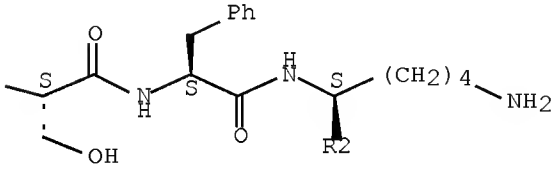

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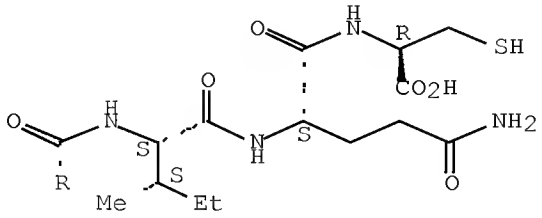

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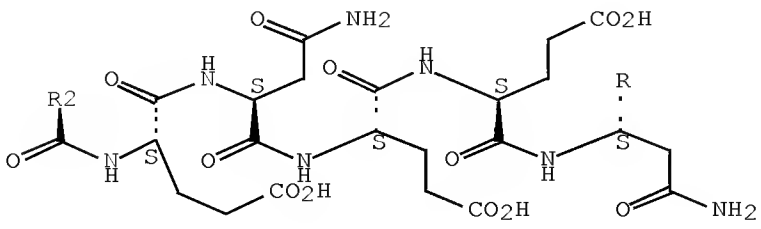

RN 864169-10-8 HCAPLUS
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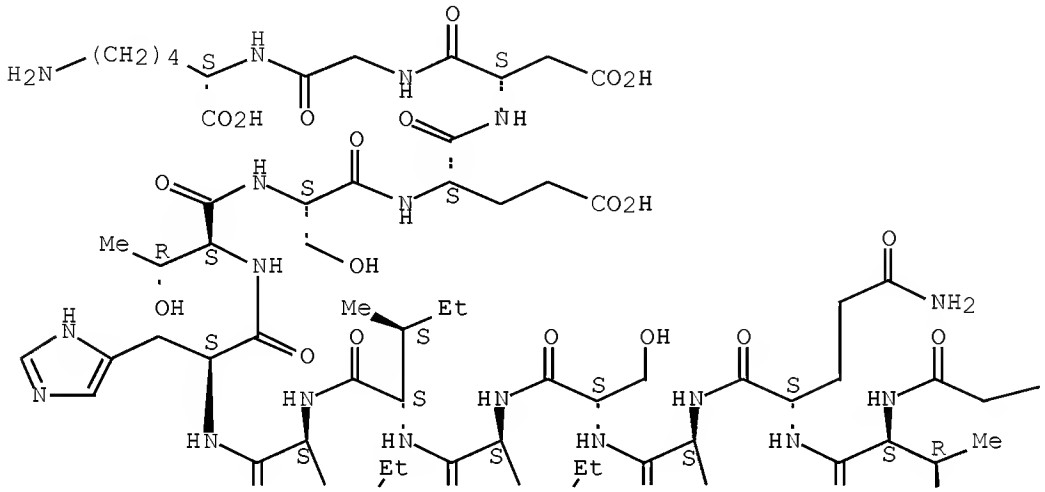
Absolute stereochemistry.

PAGE 1-A



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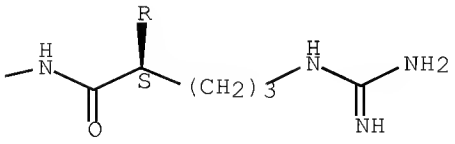

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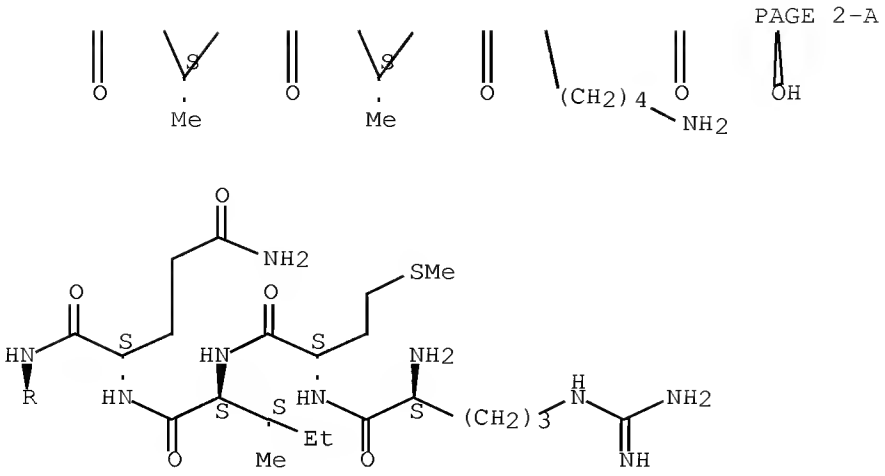
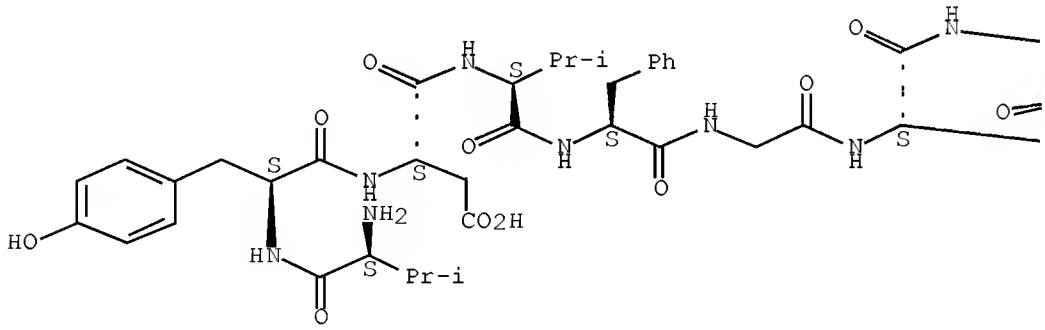


RN 864169-12-0 HCAPLUS

CN L-Isoleucine, L-valyl-L-tyrosyl-L-α-aspartyl-L-valyl-L-phenylalanylglycyl-L-lysyl-L-methionyl-L-asparaginyl-L-lysyl-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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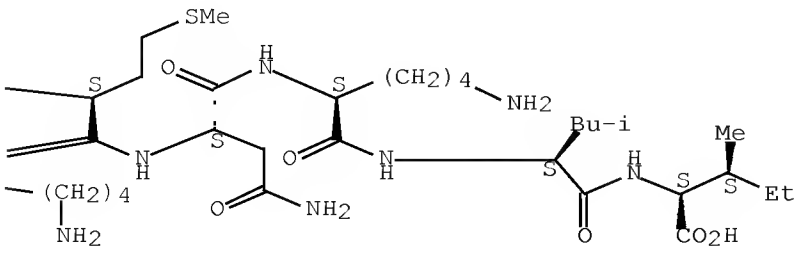

RN 864169-16-4 HCAPLUS

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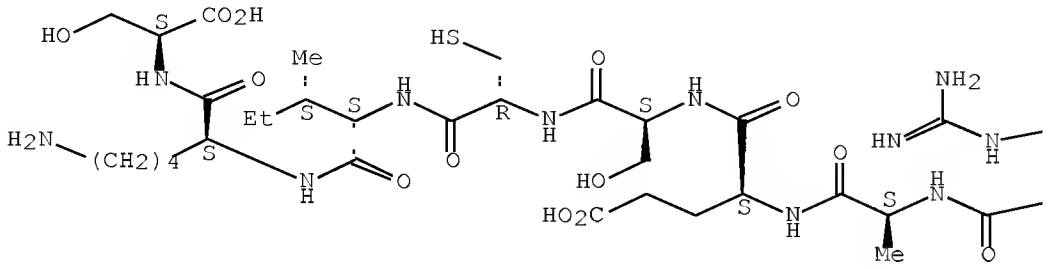
Absolute stereochemistry.

PAGE 1-A



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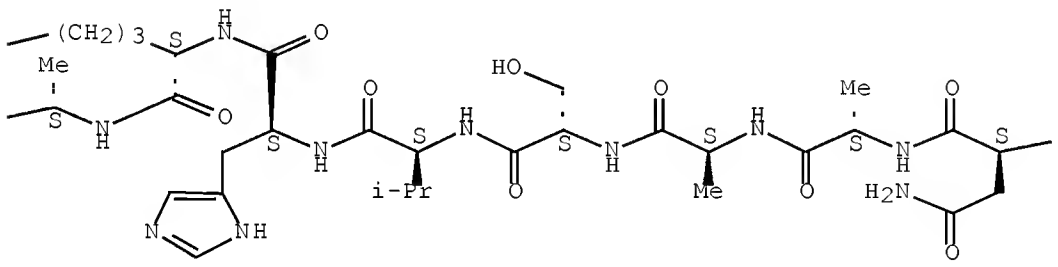

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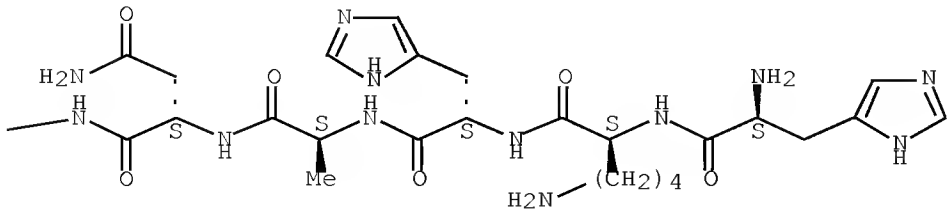

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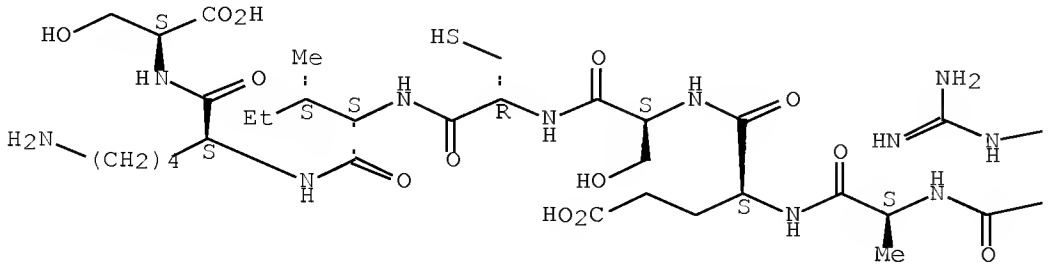
asparaginyl-L-threonyl-L-alanyl-L-seryl-L-methionyl-L-histidyl-L-arginyl-L-alanyl-L-alanyl-L-α-glutamyl-L-seryl-L-cysteinyl-L-isoleucyl-L-lysyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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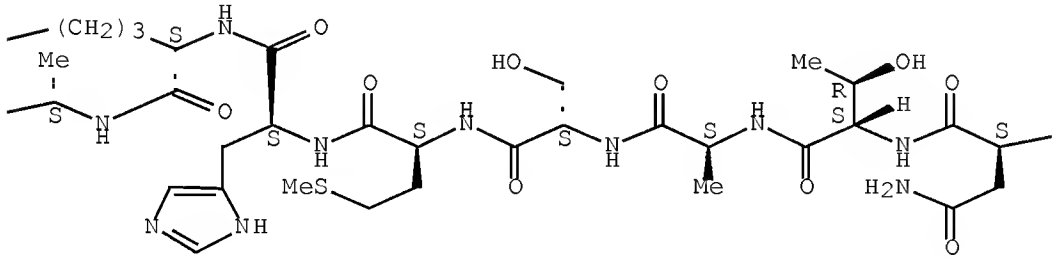

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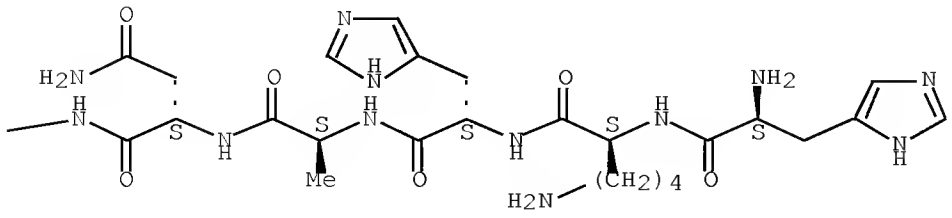
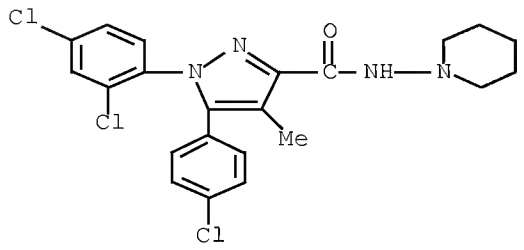


IT 168273-06-1, Rimonabant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antagonists of CB1 cannabinoid receptor for treatment of

fibrotic diseases of liver)
RN 168273-06-1 HCAPLUS
CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

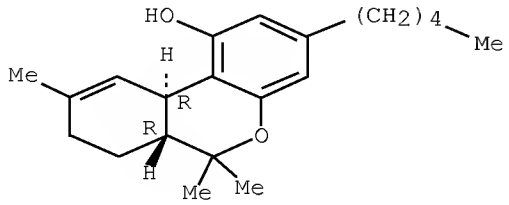
L9 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2005:572602 HCAPLUS Full-text
DOCUMENT NUMBER: 143:53581
TITLE: CB2 receptors blocks accumulation of human hepatic myofibroblasts: a novel antifibrogenic pathway in the liver
INVENTOR(S): Grenard, Pascale; Julien, Boris; Van, Nhieu Jean Tran; Mallat, Ariane; Lotersztajn, Sophie
PATENT ASSIGNEE(S): Fr.
SOURCE: U.S. Pat. Appl. Publ., 23 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20050143448	A1	20050630	US 2004-956731	20041001
US 7320805	B2	20080122		
US 20080194674	A1	20080814	US 2007-934470	20071102
US 20090221692	A1	20090903	US 2009-393927	20090226
US 7906156	B2	20110315		

PRIORITY APPLN. INFO.: US 2003-508178P P 20031001
US 2004-956731 A3 20041001
US 2007-934470 B3 20071102
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB Methods and compns. for treating diseases mediated by CB2 receptors are disclosed, including fibrosis associated with liver injury.
IT 1972-08-3, Δ9-Tetrahydrocannabinol
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CB2 receptors blocks accumulation of human hepatic myofibroblasts - novel antifibrogenic pathway in liver)
RN 1972-08-3 HCAPLUS

CN 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR,10aR)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT 7782-44-7D, Oxygen, reactive species 169592-56-7, Caspase-3 329900-75-6, Cyclooxygenase-2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CB2 receptors blocks accumulation of human hepatic myofibroblasts - novel antifibrogenic pathway in liver)
RN 7782-44-7 HCAPLUS
CN Oxygen (CA INDEX NAME)

RN 169592-56-7 HCAPLUS
CN Apopain (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 329900-75-6 HCAPLUS
CN Synthetase, prostaglandin endoperoxide, 2 (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2005:291471 HCAPLUS Full-text
DOCUMENT NUMBER: 142:441804
TITLE: Antifibrogenic role of the cannabinoid receptor CB2 in the liver
AUTHOR(S): Julien, Boris; Grenard, Pascale; Teixeira-Clerc, Fatima; Van Nhieu, Jeanne Tran; Li, Liying; Karsak, Meliha; Zimmer, Andreas; Mallat, Ariane; Lotersztajn, Sophie
CORPORATE SOURCE: INSERM, U581, Creteil, F-94010, Fr.
SOURCE: Gastroenterology (2005), 128(3), 742-755
CODEN: GASTAB; ISSN: 0016-5085
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background & Aims: Hepatic myofibroblasts are central for the development of liver fibrosis associated with chronic liver diseases, and blocking their accumulation may prevent fibrogenesis. Cannabinoids are the active components

of marijuana and act via 2 G-protein-coupled receptors, CB1 and CB2. Here, we investigated whether liver fibrogenic cells are a target of cannabinoids. Methods: CB2 receptors were characterized in biopsy specimens of normal human liver and active cirrhosis by immunohistochem., and in cultures of hepatic stellate cells and hepatic myofibroblasts by reverse-transcription polymerase chain reaction (RT-PCR), immunocytochem., and GTPγS assays. Functional studies were performed in cultured hepatic myofibroblasts and activated hepatic stellate cells. Carbon tetrachloride-induced liver fibrosis was studied in mice invalidated for CB2 receptors. Results: In liver biopsy specimens from patients with active cirrhosis of various etiologies, CB2 receptors were expressed in nonparenchymal cells located within and at the edge of fibrous septa in smooth muscle α-actin-pos. cells. In contrast, CB2 receptors were not detected in normal human liver. CB2 receptors were also detected in cultured hepatic myofibroblasts and in activated hepatic stellate cells. Their activation triggered potent antifibrogenic effects, namely, growth inhibition and apoptosis. Growth inhibition involved cyclooxygenase-2, and apoptosis resulted from oxidative stress. Finally, mice invalidated for CB2 receptors developed enhanced liver fibrosis following chronic carbon tetrachloride treatment as compared with wild-type mice. Conclusions: These data constitute the first demonstration that CB2 receptors are highly up-regulated in the cirrhotic liver, predominantly in hepatic fibrogenic cells. Moreover, this study also highlights the antifibrogenic role of CB2 receptors during chronic liver injury.

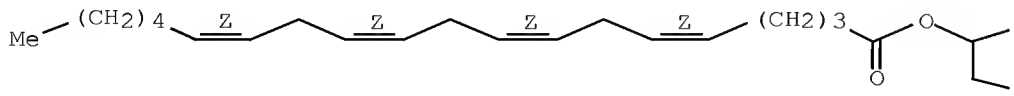
IT 53847-30-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(2-arachidonoylglycerol dose dependently inhibited DNA synthesis, elicited apoptotic effect in human hepatic myofibroblast by CB2 independent pathway)

RN 53847-30-6 HCAPLUS

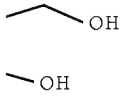
CN 5,8,11,14-Eicosatetraenoic acid, 2-hydroxy-1-(hydroxymethyl)ethyl ester, (5Z,8Z,11Z,14Z)- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

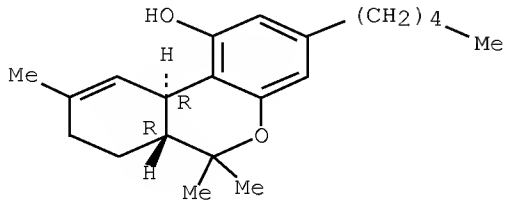


IT 1972-08-3, Tetrahydrocannabinol
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CB2 receptor was expressed in cirrhotic human liver, THC activated CB2 triggered potent anti-fibrogenic effect by growth inhibition, apoptosis in cultured human hepatic myofibroblast, activated rat hepatic stellate cell)

RN 1972-08-3 HCAPLUS

CN 6H-Dibenzo[b,d]pyran-1-ol, 6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-, (6aR,10aR)- (CA INDEX NAME)

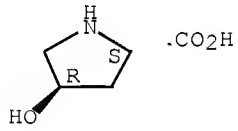
Absolute stereochemistry. Rotation (-).



IT 329900-75-6, Cyclooxygenase-2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(THC activated CB2 triggered potent anti-fibrogenic effect by growth inhibition via induction of cycooxygenase-2 in cultured human hepatic myofibroblast and in activated rat hepatic stellate cell)
RN 329900-75-6 HCAPLUS
CN Synthetase, prostaglandin endoperoxide, 2 (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT 51-35-4, Hydroxyproline
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(THC activated CB2 triggered potent anti-fibrogenic effect by growth inhibition via induction of cycooxygenase-2 in cultured human hepatic myofibroblast and in activated rat hepatic stellate cell)
RN 51-35-4 HCAPLUS
CN L-Proline, 4-hydroxy-, (4R)- (CA INDEX NAME)

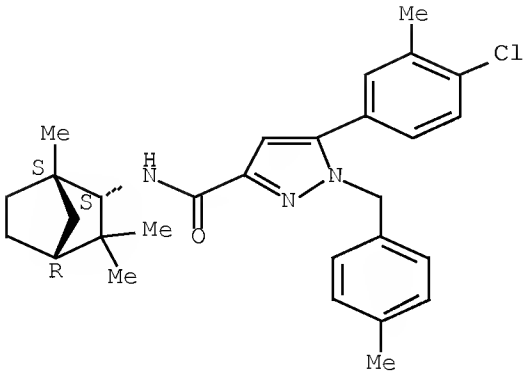
Absolute stereochemistry.



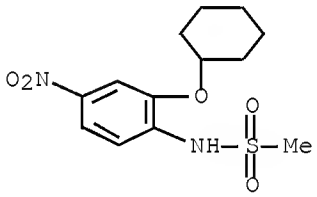
IT 169592-56-7, Caspase 3 192703-06-3, SR 144528
RL: BSU (Biological study, unclassified); BIOL (Biological1 study)
(methanandamide dose dependently inhibited DNA synthesis, elicited apoptotic effect in human hepatic myofibroblast by CB2 independent pathway)
RN 169592-56-7 HCAPLUS
CN Apopain (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 192703-06-3 HCAPLUS
CN 1H-Pyrazole-3-carboxamide, 5-(4-chloro-3-methylphenyl)-1-[(4-methylphenyl)methyl]-N-[(1S,2S,4R)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



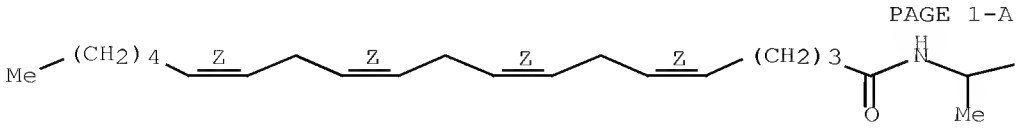
IT 123653-11-2, NS398 150314-39-9, Methanandamide
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methanandamide dose dependently inhibited DNA synthesis, elicited apoptotic effect in human hepatic myofibroblast by CB2 independent pathway)
RN 123653-11-2 HCAPLUS
CN Methanesulfonamide, N-[2-(cyclohexyloxy)-4-nitrophenyl]- (CA INDEX NAME)



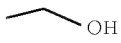
RN 150314-39-9 HCAPLUS
CN 5,8,11,14-Eicosatetraenamide, N-(2-hydroxy-1-methylethyl)-, (5Z,8Z,11Z,14Z)- (CA INDEX NAME)

Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



OS.CITING REF COUNT: 125 THERE ARE 125 CAPLUS RECORDS THAT CITE THIS

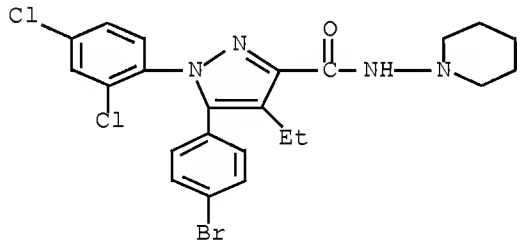
RECORD (125 CITINGS)

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

REGISTRY DISPLAY OF REQUESTED COMPOUNDS

=> d l10 1-2

L10 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2011 ACS on STN
RN 288104-79-0 REGISTRY
ED Entered STN: 01 Sep 2000
CN 1H-Pyrazole-3-carboxamide, 5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethyl-N-1-piperidinyl- (CA INDEX NAME)
OTHER NAMES:
CN 1-(2,4-Dichlorophenyl)-5-(4-bromophenyl)-4-ethyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide
CN N-(Piperidin-1-yl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethyl-1H-pyrazole-3-carboxamide
CN N-Piperidino-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethylpyrazole-3-carboxamide
CN SR 147778
CN Surinabant
MF C23 H23 Br Cl2 N4 O
CI COM
SR CA
LC STN Files: ADISINSIGHT, ANABSTR, BIOSIS, CA, CAPLUS, CASREACT, CHEMCATS, EMBASE, IMSRESEARCH, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

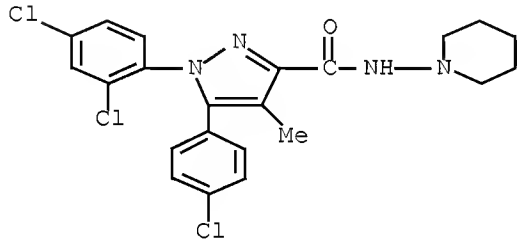


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

60 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
60 REFERENCES IN FILE CAPLUS (1907 TO DATE)
ED Entered STN: 01 Sep 2000

L10 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2011 ACS on STN
RN 168273-06-1 REGISTRY
ED Entered STN: 03 Oct 1995
CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl- (CA INDEX NAME)
OTHER NAMES:
CN 1-(2,4-Dichlorophenyl)-5-(4-chlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide
CN 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxylic acid N-(piperidin-1-yl)amide
CN 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-

pyrazole-3-carboxamide
CN A 281
CN Acomplia
CN N-Piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide
CN Rimonabant
CN SR 141716
DR 948565-21-7
MF C22 H21 Cl3 N4 O
CI COM
SR CA
LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, BIOSIS, CA, CAPLUS, CASREACT, CHEMCATS, CIN, EMBASE, IMSPATENTS, IMSRESEARCH, IPA, MRCK*, PATDPASPC, PS, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

952 REFERENCES IN FILE CA (1907 TO DATE)
10 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
969 REFERENCES IN FILE CAPLUS (1907 TO DATE)
ED Entered STN: 03 Oct 1995

RESULTS FROM SEARCHES IN REGISTRY, CAPLUS, MEDLINE, BIOSIS, EMBASE, AND DRUGU

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=> d que stat l17
L10           2 SEA FILE=REGISTRY ABB=ON  (168273-06-1 OR 288104-79-0)
L11         983 SEA FILE=HCAPLUS ABB=ON  L10
L12           8 SEA FILE=HCAPLUS ABB=ON  L11 AND ((?HEPATIC? OR ?LIVER?)(4A)?FI
                BROSIS? OR HEPATIC FIBROSIS)
L13          73 SEA L12
L14          73 DUP REMOV L12 L13 (8 DUPLICATES REMOVED)
L15           1 SEA L14 AND (PRD<20040404 OR PD<20040404)
L16          73 SEA L14 OR L15
L17          30 SEA L16 AND CB1


=> d ibib abs hitstr l17 1-30

L17  ANSWER 1 OF 30  HCAPLUS  COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER:         2009:1223535  HCAPLUS  Full-text
DOCUMENT NUMBER:          152:183122
TITLE:                    Cannabinoid receptor CB1 antagonists: state
                          of the art and challenges
AUTHOR(S):                Bifulco, Maurizio; Santoro, Antonietta; Laezza,
                          Chiara; Malfitano, Anna Maria
CORPORATE SOURCE:         Dipartimento di Scienze Farmaceutiche, Universita di
                          Salerno, Salerno, Italy
SOURCE:                   Vitamins and Hormones (San Diego, CA, United States)
                          (2009), 81(Anandamide an Endogenous Cannabinoid),
                          159-189
                          CODEN: VIHOAQ; ISSN: 0083-6729
PUBLISHER:                Elsevier Inc.
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB    A review.  The discovery of cannabinoid receptors led to the development of
      several compds. targeted against these receptors.  In particular, CB1 receptor
      antagonists have been described to possess key functions in the treatment of
      obesity and obesity-related pathologies. Numerous clin. trials revealed the
      advantage of strategies designed to block CB1 receptor but also evidenced the
      limitations due to side effects exerted by these substances.  Recent studies
      have highlighted that CB1 antagonists could have other effects and find
      applications even in other pathologies like hepatic fibrosis, chronic
      inflammatory conditions, diabetes, and cancer. Since the suspending sales of
      the lead compound, rimonabant, and the discontinuation of all ongoing clin.
      trials of CB1 blockers, alternative strategies could emerge and lead to the
      development of further basic research studies to redirect these compds.
IT    168273-06-1, Rimonabant
      RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
      (Biological study); USES (Uses)
         (rimonabat may be used in treatment of patient with obesity,
         hepatic fibrosis, chronic inflammatory conditions,
         diabetes or cancer)
RN    168273-06-1  HCAPLUS
CN    1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-
      methyl-N-1-piperidinyl-  (CA INDEX NAME)
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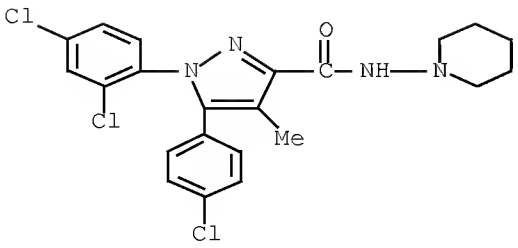


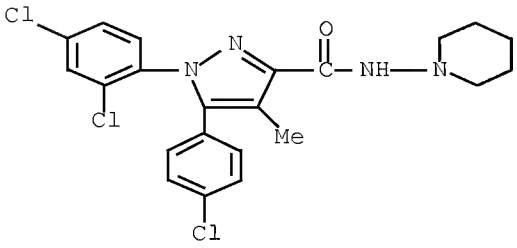
OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 131 THERE ARE 131 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 2 OF 30 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2009:897377 HCAPLUS Full-text
DOCUMENT NUMBER: 152:160720
TITLE: Cannabinoid type 1 receptor antagonism delays ascites formation in rats with cirrhosis
AUTHOR(S): Domenicali, Marco; Caraceni, Paolo; Giannone, Ferdinando; Pertosa, Anna Maria; Principe, Alessandro; Zambruni, Andrea; Trevisani, Franco; Croci, Tiziano; Bernardi, Mauro
CORPORATE SOURCE: Dipartimento di Medicina Clinica, Alma Mater Studiorum-Universita di Bologna, Bologna, Italy
SOURCE: Gastroenterology (2009), 137(1), 341-349
CODEN: GASTAB; ISSN: 0016-5085
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Endocannabinoids contribute to hemodynamic abnormalities of cirrhosis. Whether this favors renal sodium retention and ascites formation is unknown. We determined whether cannabinoid type 1 receptor antagonism prevents sodium retention and ascites formation in preascitic cirrhotic rats. Once renal sodium handling was impaired, rats with carbon tetrachloride-induced cirrhosis were randomized to receive either vehicle or rimonabant (3 [group 1] or 10 [group 2] mg/kg-1/day-1) for 2 wk. Natriuresis, sodium intake, and sodium balance were measured daily. At the end of the protocol, systemic hemodynamics, renal blood flow, ascites volume, and liver fibrosis were assessed. A significant reduction in ascites formation (group 1: 54%; group 2: 10%; vehicle: 90%) and volume (group 1: 1.6 ± 0.3 mL; group 2: 0.5 mL; vehicle: 5.5 ± 0.8 mL) occurred in treated rats. Rimonabant significantly improved sodium balance during week 2 (group 1: 0.98 ± 0.08 mmol; group 2: 0.7 ± 0.08 mmol; vehicle: 3.05 ± 0.11 mmol). Both treated groups showed lower cardiac output and higher mean arterial pressure, peripheral vascular resistance, and renal blood flow ($P < .05$). Liver fibrosis was reduced in group 2 by 30% ($P < .05$ vs vehicle). Mean arterial pressure inversely correlated with sodium balance ($R = -0.61$; $P = .003$), but not with fibrosis score. Rimonabant improves sodium balance and delays decompensation in preascitic cirrhosis. This is achieved though an improvement in systemic and renal hemodynamics, although it cannot be excluded that the antifibrotic effect of the drug may play a role.

IT 168273-06-1, Rimonabant
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rimonabant prevented sodium retention and delayed ascites formation in

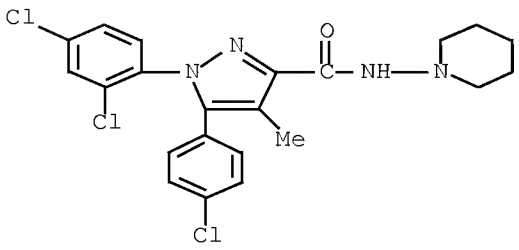
rat with cirrhosis)
RN 168273-06-1 HCAPLUS
CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl- (CA INDEX NAME)



OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 3 OF 30 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2008:1240582 HCAPLUS Full-text
DOCUMENT NUMBER: 152:560845
TITLE: Prevention of hepatic fibrosis in a murine model of metabolic syndrome with nonalcoholic steatohepatitis
AUTHOR(S): DeLeve, Laurie D.; Wang, Xiangdong; Kanel, Gary C.; Atkinson, Roscoe D.; McCuskey, Robert S.
CORPORATE SOURCE: Division of Gastrointestinal and Liver Disease and the Research Center for Liver Diseases, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
SOURCE: American Journal of Pathology (2008), 173(4), 993-1001
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The endocannabinoid pathway plays an important role in the regulation of appetite and body weight, hepatic lipid metabolism, and fibrosis. Blockade of the endocannabinoid receptor CB1 with SR141716 promotes weight loss, reduces hepatocyte fatty acid synthesis, and is antifibrotic. D-4F, an apolipoprotein A-1 mimetic with antioxidant properties, is currently in clin. trials for the treatment of atherosclerosis. C57BL/6J mice were fed a high-fat diet for 7 mo, followed by a 2.5-mo treatment with either SR141716 or D-4F. SR141716 markedly improved body weight, liver weight, serum transaminases, insulin resistance, hyperglycemia, hypercholesterolemia, hyperleptinemia, and oxidative stress, accompanied by the significant prevention of fibrosis progression. D-4F improved hypercholesterolemia and hyperleptinemia without improvement in body weight, steatohepatitis, insulin resistance, or oxidative stress, and yet, there was significant prevention of fibrosis. D-4F prevented culture-induced activation of stellate cells in vitro. In summary, C57BL/6J mice given a high-fat diet developed features of metabolic syndrome with nonalcoholic steatohepatitis and fibrosis. Both SR141716 and D-4F prevented progression of fibrosis after onset of steatohepatitis, ie, a situation comparable to a common clin. scenario, with D-4F seeming to have a more general antifibrotic effect. Either compound therefore has the potential to be of clin. benefit.

IT 168273-06-1, SR141716
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prevention of hepatic fibrosis in a murine model
of metabolic syndrome with nonalcoholic steatohepatitis)
RN 168273-06-1 HCAPLUS
CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl- (CA INDEX NAME)



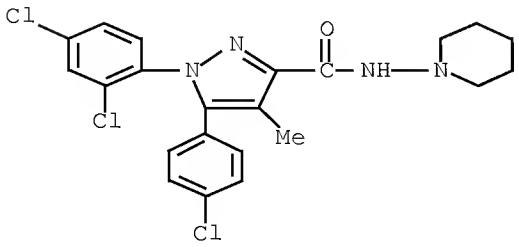
OS.CITING REF COUNT: 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (13 CITINGS)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 4 OF 30 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2008:1049101 HCAPLUS Full-text
DOCUMENT NUMBER: 150:135881
TITLE: Emerging role of cannabinoids in gastrointestinal and liver diseases: basic and clinical aspects
AUTHOR(S): Izzo, A. A.; Camilleri, M.
CORPORATE SOURCE: Department of Experimental Pharmacology, University of Naples Federico II and Endocannabinoid Research Group, Naples, Italy
SOURCE: Gut (2008), 57(8), 1140-1155
CODEN: GUTTAK; ISSN: 0017-5749
PUBLISHER: BMJ Publishing Group
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. A multitude of physiol. effects and putative pathophysiol. roles have been proposed for the endogenous cannabinoid system in the gastrointestinal tract, liver and pancreas. These range from effects on epithelial growth and regeneration, immune function, motor function, appetite control, fibrogenesis and secretion. Cannabinoids have the potential for therapeutic application in gut and liver diseases. Two exciting therapeutic applications in the area of reversing hepatic fibrosis as well as antineoplastic effects may have a significant impact in these diseases. This review critically appraises the exptl. and clin. evidence supporting the clin. application of cannabinoid receptor-based drugs in gastrointestinal, liver and pancreatic diseases. Application of modern pharmacol. principles will most probably expand the selective modulation of the cannabinoid system peripherally in humans. We anticipate that, in addition to the approval in several countries of the CB1 antagonist, rimonabant, for the treatment of obesity and associated metabolic dysfunctions, other cannabinoid modulators are likely to have an impact on human disease in the future, including hepatic fibrosis and neoplasia.
IT 168273-06-1, Rimonabant
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(cannabinoid CB1 receptor antagonist rimonabant may play role in treatment of obesity and metabolic syndrome in human)

RN 168273-06-1 HCAPLUS

CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl- (CA INDEX NAME)



OS.CITING REF COUNT: 41 THERE ARE 41 CAPLUS RECORDS THAT CITE THIS RECORD (42 CITINGS)

REFERENCE COUNT: 197 THERE ARE 197 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 5 OF 30 HCAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2008:445191 HCAPLUS Full-text

DOCUMENT NUMBER: 148:441044

TITLE: Treatment for non-alcoholic-steatohepatitis and other related diseases

INVENTOR(S): Beraza, Naiara; Dreano, Michel; Trautwein, Christian

PATENT ASSIGNEE(S): Ares Trading S.A., Switz.

SOURCE: PCT Int. Appl., 82pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

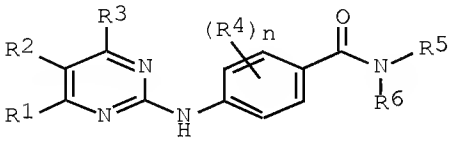
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008040548	A2	20080410	WO 2007-EP8627	20071004
WO 2008040548	A3	20090522		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
US 20080194575	A1	20080814	US 2007-906328	20071001
AU 2007304439	A1	20080410	AU 2007-304439	20071004
AU 2007304439	A2	20090423		
CA 2664413	A1	20080410	CA 2007-2664413	20071004
JP 2010505783	T	20100225	JP 2009-530804	20071004

EP 2157975 A2 20100303 EP 2007-846490 20071004
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS
PRIORITY APPLN. INFO.: US 2006-849251P P 20061004
US 2007-904116P P 20070228
WO 2007-EP8627 W 20071004
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 148:441044
GI



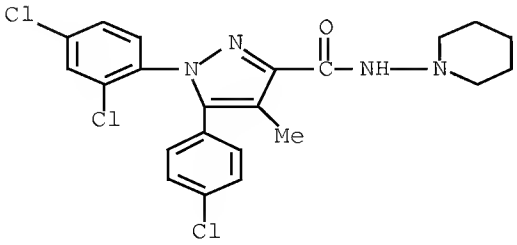
I

AB The present invention provides methods of treating a subject with non- alc. fatty liver disease (NAFLD), insulin resistance, obesity or hyperlipidemia, comprising administering to the subject an effective amount of a pyrimidin-2-ylaminobenzoyl compound I (R1 = aryl, heteroaryl; R2 = H; R3 = H, lower alkyl; R4 = halo, OH, lower alkyl, lower alkoxy; n = 0-4; R5, R6 = H, alkyl, etc., or together with the nitrogen form an optionally substituted heterocycle) or a physiol. acceptable salt thereof. The administration of Compound A (1-[4-[4-[4-(4-Chlorophenyl)pyrimidin-2- ylamino]benzoyl]piperazin-1-yl]ethanone) to mice with dietary induced NASH resulted in a clear improvement in obesity, insulin resistance, visceral fat accumulation, inflammation, lipid accumulation, lipid catabolism, oxidative stress and hepatocyte apoptosis and liver fibrosis.

IT 168273-06-1, Rimonabant
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as further therapeutic agent administered; treatment of non-alc.-steatohepatitis and related diseases with pyrimidin-2-ylaminobenzoyl compds.)

RN 168273-06-1 HCAPLUS

CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl- (CA INDEX NAME)



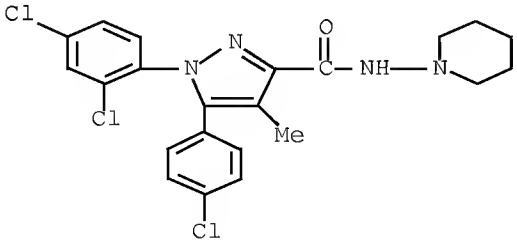
L17 ANSWER 6 OF 30 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2008:181246 HCAPLUS Full-text
DOCUMENT NUMBER: 149:214771

TITLE: The endocannabinoid system, a new pathway for treating hepatic fibrosis
AUTHOR(S): Teixeira-Clerc, F.; Julien, B.; Grenard, P.; Nhieu, J. Tran Van; Deveaux, V.; Hezode, C.; Mallat, A.; Lotersztajn, S.
CORPORATE SOURCE: Inserm, IMRB, Creteil, 94000, Fr.
SOURCE: Pathologie Biologie (2008), 56(1), 36-38
CODEN: PTBIAN; ISSN: 0369-8114
PUBLISHER: Elsevier Masson SAS
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The cannabinoid system comprises specific G protein-coupled receptors (CB1 and CB2), exogenous (marijuana-derived cannabinoids) and endogenous (endocannabinoids) ligands, and a machinery dedicated to endocannabinoid synthesis and degradation Studies over two decades have extensively documented the crucial role of the cannabinoid system in the regulation of a variety of pathophysiol. conditions. However, its role in liver pathol. has only been recently unravelled, probably given the low expression of CB1 and CB2 in the normal liver. We have recently demonstrated that CB1 and CB2 receptors display opposite effects in the regulation of liver fibrogenesis during chronic liver injury. Indeed, both receptors are up-regulated in the liver of cirrhotic patients, and expressed in liver fibrogenic cells. Moreover, CB1 receptors are profibrogenic and accordingly, the CB1 antagonist rimonabant reduces fibrosis progression in three exptl. models. In keeping with these results, daily cannabis smoking is a risk factor for fibrosis progression in patients with chronic hepatitis C. In contrast, CB2 display antifibrogenic effects, by a mechanism involving reduction of liver fibrogenic cell accumulation. These results may offer new perspectives for the treatment of liver fibrosis, combining CB2 agonist and CB1 antagonist therapy.

IT 168273-06-1, Rimonabant
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cannabinoid receptor 1 antagonist rimonabant may be useful in reducing fibrosis in patient with liver fibrosis)

RN 168273-06-1 HCAPLUS
CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl- (CA INDEX NAME)



OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 7 OF 30 HCAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2005:998698 HCAPLUS Full-text
DOCUMENT NUMBER: 143:279416

TITLE: Antagonists of the CB1 cannabinoid receptor for the treatment of fibrotic diseases of the liver
INVENTOR(S): Lotersztajn, Sophie; Mallat, Ariane; Grenard, Pascale; Julien, Boris; Nhieu, Jeanne Tran Van
PATENT ASSIGNEE(S): Institut National de la Sante et de la Recherche Medicale INSERM, Fr.
SOURCE: Eur. Pat. Appl., 25 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1574211	A1	20050914	EP 2004-290633	20040309
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK				
AU 2005218937	A1	20050915	AU 2005-218937	20050308 <--
CA 2557976	A1	20050915	CA 2005-2557976	20050308 <--
WO 2005084652	A2	20050915	WO 2005-EP3285	20050308 <--
WO 2005084652	A3	20051208		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1725223	A2	20061129	EP 2005-733278	20050308 <--
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CN 1929828	A	20070314	CN 2005-80007516	20050308 <--
BR 2005008560	A	20070814	BR 2005-8560	20050308 <--
JP 2007527893	T	20071004	JP 2007-502312	20050308 <--
RU 2402328	C2	20101027	RU 2006-134707	20050308 <--
EP 2305220	A2	20110406	EP 2010-12234	20050308 <--
EP 2305220	A3	20110518		
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
AR 48087	A1	20060329	AR 2005-100905	20050309 <--
ZA 2006007159	A	20080227	ZA 2006-7159	20060828 <--
MX 2006010287	A	20070214	MX 2006-10287	20060908 <--
IN 2006MN01194	A	20070608	IN 2006-MN1194	20061006 <--
NO 2006004603	A	20061009	NO 2006-4603	20061009 <--
US 20080214449	A1	20080904	US 2007-598736	20070719 <--

PRIORITY APPLN. INFO.:	EP 2004-290633	A	20040309 <--
	EP 2005-733278	A3	20050308
	WO 2005-EP3285	W	20050308

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

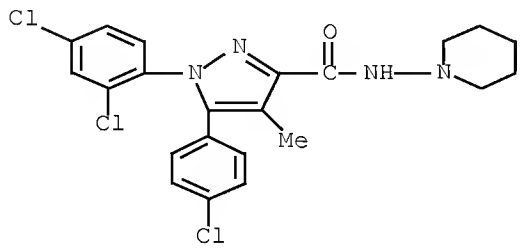
AB The invention relates to the use of antagonists to the CB1 cannabinoid receptor for the preparation of a composition for the treatment of hepatic diseases and preferably to the use of Rimonabant (N-piperidino-5-(4-chlorophenyl)-1-(2, 4-dichloropenyl)-4-methylpyrazole-3-carboxamide). The mRNA for the CB1 receptor is more abundant in cirrhotic liver than in healthy

liver. Mice lacking the CB1 receptor are more resistant to fibrotic change in the liver.

IT 168273-06-1, Rimonabant
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antagonists of CB1 cannabinoid receptor for treatment of fibrotic diseases of liver)

RN 168273-06-1 HCAPLUS

CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl- (CA INDEX NAME)



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 8 OF 30 BIOSIS COPYRIGHT (c) 2011 The Thomson Corporation on STN

ACCESSION NUMBER: 2010:156390 BIOSIS Full-text

DOCUMENT NUMBER: PREV201000156390

TITLE: TREATMENT WITH AN ENDOCANNABINOID CB-1 RECEPTOR ANTAGONIST MODULATES LIVER FIBROSIS IN A RAT MODEL OF ADVANCED CIRRHOSIS.

AUTHOR(S): Giannone, Ferdinando A. [Reprint Author]; Domenicali, Marco; Baldassarre, Maurizio; Di Pompo, Gemma; Bernardi, Mauro; Caraceni, Paolo

CORPORATE SOURCE: Univ Bologna, Dipartimento Genet Clin, Bologna, Italy

SOURCE: Hepatology, (OCT 2009) Vol. 50, No. 4, Suppl. S, pp. 827A-828A.
Meeting Info.: 60th Annual Meeting of the American-Association-for-the-Study-of-Liver-Diseases. Boston, MA, USA. October 30 -November 03, 2009. Amer Assoc Study Liver Dis.
CODEN: HPTLD9. ISSN: 0270-9139.

DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)

LANGUAGE: English

ENTRY DATE: Entered STN: 17 Mar 2010
Last Updated on STN: 17 Mar 2010

L17 ANSWER 9 OF 30 BIOSIS COPYRIGHT (c) 2011 The Thomson Corporation on STN

ACCESSION NUMBER: 2009:565445 BIOSIS Full-text

DOCUMENT NUMBER: PREV200900566548

TITLE: CANNABINOID RECEPTOR CB1 ANTAGONISTS: STATE OF THE ART AND CHALLENGES.

AUTHOR(S): Bifulco, Maurizio [Reprint Author]; Santoro, Antonietta; Laezza, Chiara; Malfitano, Anna Maria

CORPORATE SOURCE: Univ Salerno, Dipartimento Sci Farmaceut, I-84100 Salerno, Italy

SOURCE: Litwack, G [Editor]. Vitam. Horm. (N. Y.), (2009) pp. 159-189. Vitamins and Hormones: Anandamide an Endogenous Cannabinoid.
Publisher: ELSEVIER ACADEMIC PRESS INC, 525 B STREET, SUITE 1900, SAN DIEGO, CA 92101-4495 USA. Series: Vitamins and Hormones.
CODEN: VIHOAQ. ISSN: 0083-6729. ISBN: 978-0-12-374782-2(H).
DOCUMENT TYPE: Book; (Book Chapter)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Oct 2009
Last Updated on STN: 7 Oct 2009

AB The discovery of cannabinoid receptors led to the development of several compounds targeted against these receptors. In particular, CB1 receptor antagonists have been described to possess key functions in the treatment of obesity and obesity-related pathologies. Numerous clinical trials revealed the advantage of strategies designed to block CB1 receptor but also evidenced the limitations due to side effects exerted by these substances. Recent studies have highlighted that CB1 antagonists could have other effects and find applications even in other pathologies like hepatic fibrosis, chronic inflammatory conditions, diabetes, and cancer. Since the suspending sales of the lead compound, rimonabant, and the discontinuation of all ongoing clinical trials of CB1 blockers, alternative strategies could emerge and lead to the development of further basic research studies to redirect these compounds.

L17 ANSWER 10 OF 30 BIOSIS COPYRIGHT (c) 2011 The Thomson Corporation on STN
ACCESSION NUMBER: 2008:619624 BIOSIS Full-text
DOCUMENT NUMBER: PREV200800619623
TITLE: Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures - A short review.
AUTHOR(S): Svizenska, Ivana [Reprint Author]; Dubovy, Petr; Sulcova, Alexandra
CORPORATE SOURCE: Masaryk Univ, Fac Med, Div Neuroanat, Dept Anat, Kamenice 3, CZ-62500 Brno, Czech Republic
isvizen@med.muni.cz
SOURCE: Pharmacology Biochemistry and Behavior, (OCT 2008) Vol. 90, No. 4, pp. 501-511.
CODEN: PBBHAU. ISSN: 0091-3057.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Nov 2008
Last Updated on STN: 5 Nov 2008

AB In the last 25 years data has grown exponentially dealing with the discovery of the endocannabinoid system consisting of specific cannabinoid receptors, their endogenous ligands, and enzymatic systems of their biosynthesis and degradation. Progress is being made in the development of novel agonists and antagonists with receptor subtype selectivity which should help in providing a greater understanding of the physiological role of the endocannabinoid system and perhaps also in a broad number of pathologies. This could lead to advances with important therapeutic potential of drugs modulating activity of endocannabinoid system as hypnotics, analgesics, antiemetics, antiasthmatics, antihypertensives, immunomodulatory drugs, antiphlogistics, neuroprotective agents, antiepileptics, agents influencing glaucoma, spasticity and other "movement disorders", eating disorders, alcohol withdrawal, hepatic fibrosis, bone growth, and atherosclerosis. The aim of this review is to highlight distribution of the CB I and CB2 receptor subtypes in the nervous system and

functional involvement of their specific ligands. (c) 2008 Elsevier Inc. All rights reserved.

L17 ANSWER 11 OF 30 BIOSIS COPYRIGHT (c) 2011 The Thomson Corporation on STN

ACCESSION NUMBER: 2008:440435 BIOSIS Full-text
DOCUMENT NUMBER: PREV200800440434
TITLE: Effect of cannabinoid CB1-receptor antagonism on ascitic decompensation of rats with preascitic cirrhosis.
AUTHOR(S): Domenicali, M. [Reprint Author]; Caraceni, P.; Pertosa, A. M.; Giannone, F.; Principe, A.; Zambruni, A.; Trevisani, F.; Bernardi, M.
CORPORATE SOURCE: Univ Bologna, CRBA, Bologna, Italy marco.domenicali@libero.it
SOURCE: Journal of Hepatology, (2008) Vol. 48, No. Suppl. 2, pp. S38-S39.
Meeting Info.: 43rd Annual Meeting of the European-Association-for-the-Study-of-the-Liver. Milan, ITALY. April 23 -27, 2008. European Assoc Study Liver.
CODEN: JOHEEC. ISSN: 0168-8278.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Aug 2008
Last Updated on STN: 13 Aug 2008

L17 ANSWER 12 OF 30 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2011176504 EMBASE Full-text
TITLE: Marijuana-based drugs: Innovative therapeutics or designer drugs of abuse?.
AUTHOR: Seely, Kathryn A.; Prather, Paul L.; Moran, Jeffery H.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR 72205, United States. jeffery.moran@arkansas.gov
AUTHOR: James, Laura P.
CORPORATE SOURCE: Department of Pediatrics, University of Arkansas for Medical Sciences, Arkansas Children's Hospital, Little Rock, AR 72202, United States.
AUTHOR: Moran, Jeffery H.
CORPORATE SOURCE: Arkansas Department of Health, Public Health Laboratory, Little Rock, AR 72205, United States. jeffery.moran@arkansas.gov
AUTHOR: Seely, K. A., Dr. (correspondence)
CORPORATE SOURCE: Department of Pharmacology and Toxicology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR 72205, United States.
SOURCE: Molecular Interventions, (February 2011) Vol. 11, No. 1, pp. 36-51.
Refs: 126
ISSN: 1534-0384; E-ISSN: 1543-2548 CODEN: MIONAR
PUBLISHER: American Society for Pharmacology and Experimental Therapy, 9650 Rockville Pike, Bethesda, MD 20814, United States.
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles

040 Drug Dependence, Alcohol Abuse and Alcoholism
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Apr 2011
Last Updated on STN: 12 Apr 2011

AB Marijuana has been used recreationally and medicinally for centuries. The principle psychoactive component, Δ9-tetrahydrocannabinol (Δ9-THC), activates CB1 cannabinoid receptors (CB1Rs). CB1R agonists and antagonists could potentially treat a wide variety of diseases; unfortunately, therapeutic doses produce unacceptable psychiatric effects. "K2" or "Spice" (K2/Spice), an emerging drug of abuse, exhibits psychotropic actions via CB1R activation. Because of structural dissimilarity to Δ9-THC, these drugs are widely unregulated and touted as "legal" marijuana. This review summarizes current and future therapeutic uses of CB1R ligands and provides a historical perspective of the K2/Spice "phenomenon" so the reader can decide if marijuana-based drugs will truly provide innovative therapeutics or instead perpetuate drug abuse.

L17 ANSWER 13 OF 30 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2011163201 EMBASE Full-text
TITLE: Endocannabinoids in the pathophysiology of obesity - The liver.
AUTHOR: Mallat, Ariane; Lotersztajn, Sophie (correspondence)
CORPORATE SOURCE: Inserm, U955, Creteil, F-94000, France. sophie.lotersztajn@inserm.fr
AUTHOR: Mallat, Ariane; Lotersztajn, Sophie (correspondence)
CORPORATE SOURCE: Universite Paris-Est, Faculte de Medecine, UMR-S955, Creteil, F-94000, France. sophie.lotersztajn@inserm.fr
AUTHOR: Mallat, Ariane; Lotersztajn, Sophie (correspondence)
CORPORATE SOURCE: AP-HP, Groupe Henri-Mondor Albert Chenevier, Dept of Hepatology and Gastroenterology, Creteil, F-94000, France. sophie.lotersztajn@inserm.fr
SOURCE: Drug Discovery Today: Disease Mechanisms, (Winter 2010) Vol. 7, No. 3-4, pp. e185-e190.
Refs: 48
ISSN: 1740-6765
PUBLISHER: Elsevier Ltd, Langford Lane, Kidlington, Oxford, OX5 1GB, United Kingdom.
PUBLISHER IDENT.: S 1740-6765(10)00038-6
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
005 General Pathology and Pathological Anatomy
006 Internal Medicine
017 Public Health, Social Medicine and Epidemiology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 31 Mar 2011
Last Updated on STN: 31 Mar 2011

AB With the increasing prevalence of obesity and co-morbidities, non-alcoholic fatty liver disease (NAFLD) has become the most common cause of liver disease in Western countries. Clinical and experimental studies have identified CB1 and CB2 receptors as potential novel therapeutic targets in the management of NAFLD. CB2 receptors in the adipose tissue probably participate in the pathogenesis of obesity-associated insulin resistance and non-alcoholic fatty liver disease. However, hepatic CB2 receptors display beneficial effects in

various aspects of liver disease, including liver injury, regeneration and fibrosis. Hence, additional preclinical studies are warranted to define the contribution of adipose tissue versus liver CB2 receptors during chronic liver diseases. Although the development of CB1 antagonists has recently been suspended due to an alarming rate of mood disorders, preliminary preclinical data obtained with peripheral CB1 antagonists give real hopes in the development of active CB1 molecules devoid of central adverse effects. .COPYRGT. 2010 Elsevier Ltd.

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ACCESSION NUMBER: 2011044134 EMBASE Full-text
TITLE: Endocannabinoids in liver disease.
AUTHOR: Tam, Joseph; Liu, Jie; Mukhopadhyay, Bani; Cinar, Resat; Godlewski, Grzegorz; Kunos, George (correspondence)
CORPORATE SOURCE: National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, 5625 Fishers Lane, MSC-9413, Bethesda, MD 20892-9413, United States. gkunos@mail.nih.gov
SOURCE: Hepatology, (January 2011) Vol. 53, No. 1, pp. 346-355.
Refs: 107
ISSN: 0270-9139; E-ISSN: 1527-3350 CODEN: HPTLD9
PUBLISHER: John Wiley and Sons Ltd, Southern Gate, Chichester, West Sussex, PO19 8SQ, United Kingdom.
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 1 Feb 2011
Last Updated on STN: 1 Feb 2011

AB Endocannabinoids are lipid mediators of the same cannabinoid (CB) receptors that mediate the effects of marijuana. The endocannabinoid system (ECS) consists of CB receptors, endocannabinoids, and the enzymes involved in their biosynthesis and degradation, and it is present in both brain and peripheral tissues, including the liver. The hepatic ECS is activated in various liver diseases and contributes to the underlying pathologies. In patients with cirrhosis of various etiologies, the activation of vascular and cardiac CB1 receptors by macrophage-derived and platelet-derived endocannabinoids contributes to the vasodilated state and cardiomyopathy, which can be reversed by CB1 blockade. In mouse models of liver fibrosis , the activation of CB1 receptors on hepatic stellate cells is fibrogenic, and CB1 blockade slows the progression of fibrosis. Fatty liver induced by a high-fat diet or chronic alcohol feeding depends on the activation of peripheral receptors, including hepatic CB1 receptors, which also contribute to insulin resistance and dyslipidemias. Although the documented therapeutic potential of CB1 blockade is limited by neuropsychiatric side effects, these may be mitigated by using novel, peripherally restricted CB1 antagonists. .COPYRGT. 2010 American Association for the Study of Liver Diseases.

L17 ANSWER 15 OF 30 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2010289187 EMBASE Full-text
TITLE: Endocannabinoids and their role in fatty liver disease.
AUTHOR: Mallat, A. (correspondence)

CORPORATE SOURCE: AP-HP, Groupe Hospitalier Henri Mondor-Albert Chenevier, Service d'Hepatologie et de Gastroenterologie, Creteil, France. ariane.mallat@hmn.aphp.fr
AUTHOR: Mallat, A. (correspondence); Lotersztajn, S.
CORPORATE SOURCE: INSERM, U955, Creteil, France. ariane.mallat@hmn.aphp.fr
AUTHOR: Mallat, A. (correspondence); Lotersztajn, S.
CORPORATE SOURCE: Universite Paris XII-Val de Marne, Creteil, France. ariane.mallat@hmn.aphp.fr
AUTHOR: Mallat, A. (correspondence)
CORPORATE SOURCE: AP-HP, Service d'Hepatologie et de Gastroenterologie, Hopital Henri Mondor, FR-94000 Creteil, France. ariane.mall at@hmn.aphp.fr
SOURCE: Digestive Diseases, (May 2010) Vol. 28, No. 1, pp. 261-266. Refs: 53
ISSN: 0257-2753 CODEN: DIDIEW
PUBLISHER: S. Karger AG, Allschwilerstrasse 10, P.O. Box, Basel, CH-4009, Switzerland.
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 5 Jul 2010
Last Updated on STN: 5 Jul 2010

AB The endocannabinoid system comprises receptors, CB1 and CB2, their endogenous lipidic ligands and machinery dedicated to endocannabinoid synthesis and degradation. An overactive endocannabinoid system appears to contribute to the pathogenesis of several diseases, including liver diseases. With the increasing incidence of non-alcoholic fatty liver disease (NAFLD) in parallel with the obesity epidemic, the development of effective therapies is gaining considerable interest. Several recent experimental lines of evidence identify CB receptors as potential novel therapeutic targets in the management of NAFLD. Endogenous activation of peripheral CB1 receptors is a key mediator of insulin resistance and enhances liver lipogenesis in experimental models of NAFLD. Moreover, we have shown that adipose tissue CB2 receptors are markedly upregulated and promote fat inflammation, thereby contributing to insulin resistance and liver steatosis. Data from our group also indicate that tonic activation of CB1 receptors is responsible for progression of liver fibrosis, whereas CB2 receptors display anti-fibrogenic properties. The clinical relevance of these findings is supported by studies in patients with chronic hepatitis C indicating that daily cannabis use is an independent predictor of both fibrosis and steatosis severity. Moreover, preliminary data derived from clinical trials strongly suggest that selective CB1 antagonism improves insulin resistance and reduces liver fat. Tempering these promises, the first generation of CB1 antagonists raised concern due to an alarming rate of mood disorders and the development program of these molecules was suspended. Current research efforts are therefore focused on developing formulations of CB1 antagonists that do not enter the central nervous system, and preliminary experimental data obtained with such molecules are encouraging. Copyright .COPYRGT. 2010 S. Karger AG, Basel.

L17 ANSWER 16 OF 30 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2010050981 EMBASE Full-text
TITLE: Toward the design of cannabinoid CB1 receptor inverse agonists and neutral antagonists.

AUTHOR: Reggio, Patricia H.
CORPORATE SOURCE: Department of Chemistry and Biochemistry, Center for Drug Discovery, University of North Carolina Greensboro, Greensboro, NC 27402, United States. phreggio@uncg.edu
AUTHOR: Reggio, P. H. (correspondence)
CORPORATE SOURCE: Department of Chemistry and Biochemistry, Center for Drug Discovery, University of North Carolina Greensboro, Greensboro, NC 27402, United States. phreggio@uncg.edu
SOURCE: Drug Development Research, (December 2009) Vol. 70, No. 8, pp. 585-600.
Refs: 106
ISSN: 0272-4391; E-ISSN: 1098-2299 CODEN: DDREDK
PUBLISHER: Wiley-Liss Inc., 111 River Street, Hoboken, NJ 07030-5774, United States.
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Mar 2010
Last Updated on STN: 2 Mar 2010

AB The cannabinoid CB1 receptor belongs to Class A of the G-protein-coupled receptor (GPCR) family. The high constitutive activity of CB1 facilitates inverse agonism at this receptor, and CB1 inverse agonists/antagonists have recently been considered for the treatment of obesity and metabolic syndrome. GPCRs are assumed to have a common topology and to share a common molecular activation mechanism involving their intracellular domains. However, each individual receptor will also have a molecular switch within the ligand binding pocket that is a noncovalent intramolecular interaction in the basal state of the GPCR that must be disrupted to achieve an active state or stabilized to maintain the inactive state. Knowledge of the molecular switch within the ligand binding pocket can greatly facilitate the rational design of inverse agonists and neutral antagonists. This review begins with a brief review on the CB1 receptor and its ligands. The review then focuses on the experimental literature on GPCR structure and activation in Class A receptors. The identification of the molecular switch region in the ligand binding pocket of CB1 (F3.36/W6.48) is discussed and the combined mutation and modeling studies that have led to the identification of interactions key to the inverse agonism of SR141716A are presented. Finally, the development of the first CB1 neutral antagonists based on these modeling/mutation results is discussed. .COPYRGT. 2009 Wiley-Liss, Inc.

L17 ANSWER 17 OF 30 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2009332499 EMBASE Full-text
TITLE: From endocannabinoid profiling to 'endocannabinoid therapeutics'.
AUTHOR: Ligresti, Alessia (correspondence); Petrosino, Stefania; Di Marzo, Vincenzo
CORPORATE SOURCE: Endocannabinoid Research Group, Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, Via Campi Flegrei 34, 80078 Pozzuoli, Naples, Italy. vdimarzo@icmib.na.cnr.it
SOURCE: Current Opinion in Chemical Biology, (June 2009) Vol. 13, No. 3, pp. 321-331.
Refs: 134
ISSN: 1367-5931 CODEN: COCBF4

PUBLISHER: Elsevier Ltd, Langford Lane, Kidlington, Oxford, OX5 1GB, United Kingdom.
PUBLISHER IDENT.: S 1367-5931(09)00060-X
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 24 Aug 2009
Last Updated on STN: 24 Aug 2009

AB The discovery of the endocannabinoid signalling system, that is, of cannabinoid receptors, their endogenous ligands, known as endocannabinoids, and of endocannabinoid anabolic and catabolic enzymes, raised several questions regarding the physiopathological role of these mediators. Several of these questions were answered by investigating alterations in the levels of the most studied endocannabinoids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), in tissues of animal models of disorders, and in bioptic samples and biological fluids (cerebrospinal fluid and blood) of human volunteers. Subsequently, the pharmacological effects of synthetic compounds that selectively target the cannabinoid CB1 and CB2 receptors, and endocannabinoid anabolic and catabolic enzymes, established cause-effect relationships between pathological alterations in endocannabinoid levels and the symptoms and progress of several disorders, including emesis, obesity, metabolic disorders, hepatic diseases, pain, inflammation and neurological and neuropsychiatric disorders. These new developments are discussed in this second review on the endocannabinoids, together with the results of pre-clinical and clinical studies on the potential therapeutic use of plant-derived cannabinoids and synthetic agents that manipulate pharmacologically the action at cannabinoid receptors or the tissue levels of AEA and 2-AG. .COPYRGT. 2009 Elsevier Ltd. All rights reserved.

L17 ANSWER 18 OF 30 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2009289426 EMBASE Full-text
TITLE: Synthesis and pharmacological activity of a potent inhibitor of the biosynthesis of the endocannabinoid 2-arachidonoylglycerol.
AUTHOR: Bisogno, Tiziana; Allara, Marco; Di Marzo, Vincenzo (correspondence)
CORPORATE SOURCE: Endocannabinoid Research Group, Institute of Biomolecular Chemistry, Consiglio Nazionale Delle Ricerche, Via Campi Flegrei 34, Comprensorio Olivetti, Pozzuoli (NA), Italy. vdimarzo@icmib.na.cnr.it
AUTHOR: Burston, James J.; Wiley, Jenny L.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, Virginia Commonwealth University, 410 North 12th St., Richmond, VA 23298, United States.
AUTHOR: Rai, Ravi; Saha, Bijali; Mahadevan, Anu; Razdan, Raj K.
CORPORATE SOURCE: Organix Inc., 240 Salem St., Woburn, MA 01801, United States.
SOURCE: ChemMedChem, (8 Jun 2009) Vol. 4, No. 6, pp. 946-950.
Refs: 23
ISSN: 1860-7179; E-ISSN: 1860-7187
PUBLISHER: John Wiley and Sons Ltd, Southern Gate, Chichester, West Sussex, PO19 8SQ, United Kingdom.
COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 13 Jul 2009
Last Updated on STN: 13 Jul 2009

AB (Chemical Equation Presented) Biosynthesis Inhibition: O-5596, a new inhibitor of the biosynthesis of the endocannabinoid, 2-arachidonoylglycerol, was synthesized and found to be potent (IC50=100 nm) and selective versus other proteins and enzymes of the endocannabinoid system in vitro and active in vivo at reducing food intake in mice. .COPYRGT. 2009 Wiley-VCH Verlag GmbH & Co. KGaA.

L17 ANSWER 19 OF 30 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2009159673 EMBASE Full-text
TITLE: Role of cannabinoids in chronic liver diseases.
AUTHOR: Parfieniuk, Anna; Flisiak, Robert (correspondence)
CORPORATE SOURCE: Department of Infectious Diseases and Hepatology, Medical University of Bialystok, Zurawia Str. 14, Bialystok 15-540, Poland. flisiakr@poczta.onet.pl
SOURCE: World Journal of Gastroenterology, (28 Oct 2008) Vol. 14, No. 40, pp. 6109-6114.
Refs: 41
ISSN: 1007-9327 CODEN: WJGAF2
PUBLISHER: WJG Press, P.O. Box 2345, Beijing, 100023, China.
COUNTRY: China
DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 008 Neurology and Neurosurgery
018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 14 Apr 2009
Last Updated on STN: 14 Apr 2009

AB Cannabinoids are a group of compounds acting primarily via CB1 and CB2 receptors. The expression of cannabinoid receptors in normal liver is low or absent. However, many reports have proven up-regulation of the expression of CB1 and CB2 receptors in hepatic myofibroblasts and vascular endothelial cells, as well as increased concentration of endocannabinoids in liver in the course of chronic progressive liver diseases. It has been shown that CB1 receptor signalling exerts profibrogenic and proinflammatory effects in liver tissue, primarily due to the stimulation of hepatic stellate cells, whereas the activation of CB2 receptors inhibits or even reverses liver fibrogenesis. Similarly, CB1 receptor stimulation contributes to progression of liver steatosis. In end-stage liver disease, the endocannabinoid system has been shown to contribute to hepatic encephalopathy and vascular effects, such as portal hypertension, splanchnic vasodilatation, relative peripheral hypotension and probably cirrhotic cardiomyopathy. So far, available evidence is based on cellular cultures or animal models. Clinical data on the effects of cannabinoids in chronic liver diseases are limited. However, recent studies have shown the contribution of cannabis smoking to the progression of liver fibrosis and steatosis. Moreover, controlling CB1 or CB2 signalling

appears to be an attractive target in managing liver diseases. .COPYRGT. 2008 The WJG Press. All rights reserved.

L17 ANSWER 20 OF 30 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2009110450 EMBASE Full-text
TITLE: The role of the endocannabinoid system in liver diseases.
AUTHOR: Caraceni, Paolo, Dr. (correspondence); Domenicali, Marco; Giannone, Ferdinando; Bernardi, Mauro
CORPORATE SOURCE: Department of Clinical Medicine, Center for Applied Biomedical Research (C.R.B.A.), Alma Mater Studiorum University of Bologna, Via Massarenti 9, 40138 Bologna, Italy. paolo.caraceni@unibo.it
SOURCE: Best Practice and Research: Clinical Endocrinology and Metabolism, (February 2009) Vol. 23, No. 1, pp. 65-77. Refs: 69
ISSN: 1521-690X CODEN: BPRCE9
PUBLISHER: Bailliere Tindall Ltd, 32 Jamestown Road, London, NW1 7BY, United Kingdom.
PUBLISHER IDENT.: S 1521-690X(08)00137-1
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 003 Endocrinology
005 General Pathology and Pathological Anatomy
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
048 Gastroenterology
FILE SEGMENT:ClinicalTrials.gov
CLINICAL TRIAL NO.: NCT00576667
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20 Mar 2009
Last Updated on STN: 20 Mar 2009

AB Endogenous cannabinoids (ECs) are ubiquitous lipid signaling molecules provided by a number of central and peripheral effects, which are mediated mainly by the specific receptors CB1 and CB2. In the last decade a considerable number of studies has shown that ECs and their receptors play an important role in the pathophysiology of liver diseases. The EC system is strongly up-regulated during chronic liver diseases. Until now it has been implicated in the pathogenesis of fatty liver disease associated with obesity, alcohol abuse, and hepatitis C, in the progression of fibrosis to cirrhosis, and in the development of portal hypertension, hyperdynamic circulatory syndrome and its complications, and cirrhotic cardiomyopathy. Furthermore, the EC system can participate in the pathogenesis of acute liver injury by modulating the mechanisms responsible for cell injury and inflammatory response. Thus, targeting the CB1 and CB2 receptors represents a potential therapeutic goal for the treatment of liver diseases. .COPYRGT. 2008 Elsevier Ltd. All rights reserved.

L17 ANSWER 21 OF 30 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2009044766 EMBASE Full-text
TITLE: Cannabinoid receptors as therapeutic targets in the management of liver diseases.
AUTHOR: Mallat, Ariane, Prof. Dr. (correspondence); Lotersztajn, Sophie
CORPORATE SOURCE: INSERM U841, Service d'Hepatologie, Hospital Henri Moudor,

94000 Creteil, France. ariane.mallat@hmn.aphp.fr
AUTHOR: Mallat, Ariane, Prof. Dr. (correspondence)
CORPORATE SOURCE: Service d'Hepatologie et de Gastroenterologie, INSERM U 841, Institut Mondor de recherche Biomedicale Hopital Henri Mondor, 94000 Creteil, France. ariane.mallat@hmn.aphp.fr
SOURCE: Drug News and Perspectives, (September 2008) Vol. 21, No. 7, pp. 363-368.
Refs: 54
ISSN: 0214-0934 CODEN: DNPEED
PUBLISHER: Prous Science, P.O. Box 540, Barcelona, 08080, Spain.
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 004 Microbiology: Bacteriology, Mycology, Parasitology and Virology
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 Feb 2009
Last Updated on STN: 18 Feb 2009

AB Despite recent advances in the understanding of mechanisms underlying the pathogenesis of liver diseases, therapeutic agents are still needed in several instances such as nonalcoholic fatty liver disease, alcoholic liver disease or fibrogenesis associated with chronic liver injury. Over the past decades, cannabinoid receptors have emerged as critical mediators of acute and chronic liver injury, and pharmacological modulation of these receptors has demonstrated efficacy in preclinical models of nonalcoholic and alcoholic fatty liver, fibrosis, liver ischemia reperfusion and of complications of cirrhosis, including cirrhotic portal hypertension, cirrhotic cardiomyopathy and hepatic encephalopathy. Mcreover, CB1 antagonists have entered clinical trials for the management of nonalcoholic steatohepatitis. This review will depict the pleiotropic functions of cannabinoid receptors in liver disease and highlight potential therapeutic applications, some of which may be available in the near future. .COPYRGT. 2008 Prous Science, S.A.U. or its licensors.
All rights reserved.

L17 ANSWER 22 OF 30 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2008191472 EMBASE Full-text
TITLE: The endocannabinoid system and liver diseases.
AUTHOR: Caraceni, Paolo (correspondence); Domenicali, M.; Bernardi, M.
CORPORATE SOURCE: Department of Internal Medicine, Cardioangiology, Hepatology, Alma Mater Studiorum University of Bologna, Via Massarenti 9, 40138 Bologna, Italy. paolo.caraceni@unibo.it
AUTHOR: Caraceni, Paolo (correspondence); Domenicali, M.; Bernardi, M.
CORPORATE SOURCE: Center for Applied Biomedical Research (CRBA), S. Orsola-Malpighi University Hospital, Bologna, Italy. paolo.caraceni@unibo.it
AUTHOR: Caraceni, Paolo (correspondence)
CORPORATE SOURCE: Dipartimento di Medicina Interna, Cardioangiologia, Epatologia, Universitv of Bologna, Via Massarenti 9, 40138 Bologna, Italy. paolo.caraceni@unibo.it
SOURCE: Journal of Neuroendocrinology, (May 2008) Vol. 20, No. SUPPL. 1, pp. 47-52.
Refs: 49

ISSN: 0953-8194; E-ISSN: 1365-2826 CODEN: JOUNE2
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article; (Conference paper)
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
048 Gastroenterology
052 Toxicology
FILE SEGMENT:ClinicalTrials.gov
CLINICAL TRIAL NO.: NCT00576667
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 May 2008
Last Updated on STN: 2 May 2008

AB Endogenous cannabinoids (EC) are ubiquitous lipid signalling molecules provided by a Number of central and peripheral effects, which are mainly mediated by the specific cannabinoid receptors CB1 and CB2. Although the expression of these receptors is very low or even absent in the healthy liver, a considerable series of experimental studies and some clinical observations have recognised the EC system as an important player in the pathophysiology of liver diseases. The EC system is highly up-regulated during chronic liver diseases and, to date, it has been implicated in the pathogenesis of non-alcoholic fatty liver disease, progression of fibrosis to cirrhosis and the development of the cardiovascular abnormalities of cirrhosis, such as the hyperdynamic circulatory syndrome and cirrhotic cardiomiopathy. Furthermore, the EC system influences the mechanisms responsible for cell damage and the inflammatory response during acute liver injury, such as that resulting from ischaemia-reperfusion. Thus, molecules targeting the CB1 and CB2 receptors may represent potential therapeutic agents for the treatment of liver diseases. At present, the CB1 antagonists represent the most attractive pharmaceutical tool to resolve fat accumulation in patients with non-alcoholic fatty liver disease and to treat patients with cirrhosis, as they may slow the progression of fibrosis and attenuate the cardiovascular alterations associated with the advanced stage of the disease. .COPYRGT. 2008 The Authors. Journal compilation .COPYRGT. 2008 Blackwell Publishing.

L17 ANSWER 23 OF 30 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2008180384 EMBASE Full-text
TITLE: Endocannabinoids and Liver Disease. III. Endocannabinoid effects on immune cells: Implications for inflammatory liver diseases.
AUTHOR: Pacher, Pal (correspondence)
CORPORATE SOURCE: Section on Oxidative Stress Tissue Injury, National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, United States. pacher@mail.nih.gov
AUTHOR: Gao, Bin
CORPORATE SOURCE: Section on Liver Biology, National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, United States.
AUTHOR: Pacher, Pal (correspondence)
CORPORATE SOURCE: Laboratory of Physiological Studies, National Institutes of Health, NIAAA, 5625 Fishers Lane, Bethesda, MD 20892-9413, United States. pacher@mail.nih.gov
SOURCE: American Journal of Physiology - Gastrointestinal and Liver Physiology, (Apr 2008) Vol. 294, No. 4, pp. G850-G854.
Refs: 27
ISSN: 0193-1857; E-ISSN: 1522-1547 CODEN: APGPDF
COUNTRY: United States

DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 037 Drug Literature Index
048 Gastroenterology
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 7 May 2008
Last Updated on STN: 7 May 2008

AB Recent studies have implicated dysregulation of the endocannabinoid system in various liver diseases and their complications (e.g., hepatitis, fibrosis, cirrhosis, cirrhotic cardiomyopathy, and ischemia-reperfusion), and demonstrated that its modulation by either cannabinoid 2 (CB2) receptor agonists or CB1 antagonists may be of significant therapeutic benefits. This review is aimed to focus on the triggers and sources of endocannabinoids during liver inflammation and on the novel role of CB2 receptors in the interplay between the activated endothelium and various inflammatory cells (leukocytes, lymphocytes, etc.), which play pivotal role in the early development and progression of inflammatory and other liver diseases. Copyright .COPYRGT. 2008 the American Physiological Society.

L17 ANSWER 24 OF 30 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2007441322 EMBASE Full-text
TITLE: Blocking the cannabinoid receptors: Drug candidates and therapeutic promises.
AUTHOR: Muccioli, Giulio G. (correspondence)
CORPORATE SOURCE: Department of Pharmacology, University of Washington, Seattle, WA 98195, United States. giulio.muccioli@uclouvain.be
AUTHOR: Muccioli, Giulio G. (correspondence)
CORPORATE SOURCE: Unite de Chimie Pharmaceutique et de Radiopharmacie, Universite Catholoque de Louvain, Avenue Mounier 73, B-1200 Brussels, Belgium. giulio.muccioli@uclouvain.be
SOURCE: Chemistry and Biodiversity, (2007) Vol. 4, No. 8, pp. 1805-1827.
Refs: 199
ISSN: 1612-1872; E-ISSN: 1612-1880
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
FILE SEGMENT:ClinicalTrials.gov
CLINICAL TRIAL NO.: NCT00029848; NCT00029861; NCT00075205; NCT00257257; NCT00358228; NCT00386061
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 1 Nov 2007
Last Updated on STN: 1 Nov 2007

AB The CB1 and CB2 cannabinoid receptors have been described as two prime sites of action for endocannabinoids. Both the localization and pharmacology of these two G-protein-coupled receptors are well-described, and numerous selective ligands have been characterized. The physiological effects of Cannabis sativa (cannabis) and a throughout study of the endocannabinoid system allowed for the identification of several pathophysiological conditions - including obesity, dyslipidemia, addictions, inflammation, and allergies - in which blocking the cannabinoid receptors might be beneficial. Many CB1 receptor antagonists are now in clinical trials, and the results of several

studies involving the CB1 antagonist lead compound rimonabant (SR141716A) are now available. This review describes the pharmacological tools that are currently available and the animal studies supporting the therapeutic use of cannabinoid receptor antagonists and inverse agonists. The data available from the clinical trials are also discussed. .COPYRGT. 2007 Verlag Helvetica Chimica Acta AG, Zurich.

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ACCESSION NUMBER: 2007317710 EMBASE Full-text
TITLE: Rimonabant: Just an antiobesity drug? Current evidence on its pleiotropic effects.
AUTHOR: Bifulco, Maurizio, Prof. (correspondence); Grimaldi, Claudia; Gazzerro, Patrizia; Pisanti, Simona; Santoro, Antonietta
CORPORATE SOURCE: Department of Pharmaceutical Sciences, University of Salerno, Via Ponte don Melillo, 84084 Fisciano, Salerno, Italy. maubiful@unisa.It
SOURCE: Molecular Pharmacology, (Jun 2007) Vol. 71, No. 6, pp. 1445-1456.
Refs: 119
ISSN: 0026-895X; E-ISSN: 1521-0111 CODEN: MOPMA3
COUNTRY: United States
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 003 Endocrinology
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 11 Jul 2007
Last Updated on STN: 11 Jul 2007

AB The advent of the highly selective cannabinoid receptor (CB1) antagonist, rimonabant (SR141716; Acomplia) can revolutionize the ability of the clinicians to manage obesity. Large-scale clinical trials have demonstrated that rimonabant therapy can reduce obesity. Although, the precise mechanisms of action of rimonabant have to be further dissected, it is emerging, from both preclinical and clinical research, that not only is rimonabant an antiobesity drug, but also its pleiotropic functions affect a broad range of diseases, from obesity-related comorbidities to drug dependence and cancer. Here we review recent data from the literature and discuss the full pharmacological potential of this drug. Copyright .COPYRGT. 2007 The American Society for Pharmacology and Experimental Therapeutics.

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ACCESSION NUMBER: 2007123819 EMBASE Full-text
TITLE: CB1 cannabinoid receptor antagonism: A new strategy for the treatment of liver fibrosis.
AUTHOR: Wasmuth, Hermann E., Dr. (correspondence); Trautwein, Christian
CORPORATE SOURCE: Medical Department III, University Hospital Aachen, RWTH Aachen, Aachen, Germany.
SOURCE: Hepatology, (Feb 2007) Vol. 45, No. 2, pp. 543-544.
Refs: 11
ISSN: 0270-9139 CODEN: HPTLD9
COUNTRY: United States

DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 022 Human Genetics
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
048 Gastroenterology
006 Internal Medicine
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Apr 2007
Last Updated on STN: 12 Apr 2007

L17 ANSWER 27 OF 30 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2007098940 EMBASE Full-text
TITLE: Cannabinoid receptors as new targets of antifibrosing strategies during chronic liver diseases.
AUTHOR: Mallat, Ariane; Teixeira-Clerc, Fatima; Deveaux, Vanessa; Lotersztajn, Sophie, Dr. (correspondence)
CORPORATE SOURCE: INSERM, Unite 841, Institut Mondor de Recherche Biomedicale, Creteil F-94000, France. Sophie.Lotersztajn@creteil.inserm.fr
AUTHOR: Mallat, Ariane; Lotersztajn, Sophie, Dr. (correspondence)
CORPORATE SOURCE: AP-HP, Groupe Hospitalier Henri-Mondor-Albert Chenevier, Service d'Hepatologie et de Gastroenterologie, Creteil F-94000, France. Sophie.Lotersztajn@creteil.inserm.fr
SOURCE: Expert Opinion on Therapeutic Targets, (Mar 2007) Vol. 11, No. 3, pp. 403-409.
Refs: 45
ISSN: 1472-8222 CODEN: EOTTAO
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 13 Mar 2007
Last Updated on STN: 13 Mar 2007

AB Chronic liver injury exposes the patient to liver fibrosis and its end stage, cirrhosis, is a major public health problem worldwide. In western countries, prevailing causes of cirrhosis include chronic alcohol consumption, hepatitis C virus infection and non-alcoholic steatohepatitis. Current treatment of hepatic fibrosis is limited to withdrawal of the noxious agent. Nevertheless, suppression of the cause of hepatic injury is not always feasible and numerous efforts are directed at the development of liver-specific antifibrotic therapies. Along these lines, the authors recently demonstrated that the endocannabinoid system shows promise as a novel target for antifibrotic therapy during chronic liver injury. Indeed, cannabinoid receptors CB1 and CB2 promote dual pro- and antifibrogenic effects, respectively. Therefore, endocannabinoid-based therapies, combining CB2 agonists and CB1 antagonists may open novel therapeutic perspectives for the treatment of chronic liver diseases. .COPYRGT. 2007 Informa UK Ltd.

L17 ANSWER 28 OF 30 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2006583977 EMBASE Full-text
TITLE: Reefer madness? Assessing the effects of cannabinoids with

a less jaundiced eye.
AUTHOR: Friedman, Scott L. (correspondence)
CORPORATE SOURCE: Division of Liver Diseases, Mount Sinai School of Medicine, 1425 Madison Avenue, Room 11-70C, New York, NY, United States. Scott.Friedman@mssm.edu
SOURCE: Journal of Hepatology, (Jan 2007) Vol. 46, No. 1, pp. 180-182.
Refs: 18
ISSN: 0168-8278 CODEN: JOHEEC
PUBLISHER IDENT.: S 0168-8278(06)00556-3
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 29 Dec 2006
Last Updated on STN: 29 Dec 2006

AB CB1 cannabinoid receptor antagonism: a new strategy for the treatment of liver fibrosis. Teixeira-Clerc F, Julien B, Grenard P, Tran Van Nhieu J, Deveaux V, Li L, Serriere-Lanneau V, Ledent C, Mallat A, Lotersztajn S. Hepatic fibrosis, the common response associated with chronic liver diseases, ultimately leads to cirrhosis, a major public health problem worldwide. We recently showed that activation of hepatic cannabinoid CB2 receptors limits progression of experimental liver fibrosis. We also found that during the course of chronic hepatitis C, daily cannabis use is an independent predictor of fibrosis progression. Overall, these results suggest that endocannabinoids may drive both CB2-mediated antifibrogenic effects and CB2-independent profibrogenic effects. Here we investigated whether activation of cannabinoid CB1 receptors (encoded by Cnr1) promotes progression of fibrosis. CB1 receptors were highly induced in human cirrhotic samples and in liver fibrogenic cells. Treatment with the CB1 receptor antagonist SR141716A decreased the wound-healing response to acute liver injury and inhibited progression of fibrosis in three models of chronic liver injury. We saw similar changes in Cnr1-/- mice as compared to wild-type mice. Genetic or pharmacological inactivation of CB1 receptors decreased fibrogenesis by lowering hepatic transforming growth factor (TGF)-β1 and reducing accumulation of fibrogenic cells in the liver after apoptosis and growth inhibition of hepatic myofibroblasts. In conclusion, our study shows that CB1 receptor antagonists hold promise for the treatment of liver fibrosis. [Abstract reproduced by permission of Nat Med 2006;12:671-676]. .COPYRGT. 2006 European Association for the Study of the Liver.

L17 ANSWER 29 OF 30 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2006278784 EMBASE Full-text
TITLE: Cannabinoids hurt, heal in cirrhosis.
AUTHOR: Kunos, George (correspondence); Osei-Hyiaman, Douglas; Batkai, Sandor; Gao, Bin
CORPORATE SOURCE: Laboratory of Physiologic Studies, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD 20892-9413, United States. gkunos@mail.nih.gov
SOURCE: Nature Medicine, (Jun 2006) Vol. 12, No. 6, pp. 608-610.
Refs: 15
ISSN: 1078-8956; E-ISSN: 1546-170X CODEN: NAMEFI
PUBLISHER IDENT.: N0606608
COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 017 Public Health, Social Medicine and Epidemiology
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 25 Jul 2006
Last Updated on STN: 25 Jul 2006

AB Marijuana receptors are present in fibrogenic cells of the liver, and their expression is induced in cirrhosis. Blockade of the CB1 subtype is now shown to inhibit fibrogenesis, offering a new approach for the treatment of cirrhosis (pages 671-676). .COPYRGT. 2006 Nature Publishing Group.

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ACCESSION NUMBER: 2006277078 EMBASE Full-text
TITLE: CB1 cannabinoid receptor antagonism: A new strategy for the treatment of liver fibrosis.
AUTHOR: Teixeira-Clerc, Fatima; Julien, Boris; Grenard, Pascale; Van Nhieu, Jeanne Tran; Deveaux, Vanessa; Li, Liying; Serriere-Lanneau, Valerie; Mallat, Ariane; Lotersztajn, Sophie (correspondence)
CORPORATE SOURCE: INSERM, Unite 581, Hopital Henri Mondor Creteil, F-9400, France. sophie.lotersztajn@creteil.inserm.fr
AUTHOR: Teixeira-Clerc, Fatima; Julien, Boris; Grenard, Pascale; Van Nhieu, Jeanne Tran; Deveaux, Vanessa; Li, Liying; Serriere-Lanneau, Valerie; Mallat, Ariane; Lotersztajn, Sophie (correspondence)
CORPORATE SOURCE: Universite Paris 12, Faculte de Medecine, Creteil, F-94000, France. sophie.lotersztajn@creteil.inserm.fr
AUTHOR: Mallat, Ariane; Lotersztajn, Sophie (correspondence)
CORPORATE SOURCE: AP-HP, Groupe Hospitalier Henri Mondor-Albert Chenevier, Service D'Hepatologie et de Gastroenterologie, Creteil, F-94000, France. sophie.lotersztajn@creteil.inserm.fr
AUTHOR: Van Nhieu, Jeanne Tran
CORPORATE SOURCE: AP-HP, Groupe Hospitalier Henri Mondor-Albert Chenevier, Departement de Pathologie, Creteil, F-94000, France.
AUTHOR: Ledent, Catherine
CORPORATE SOURCE: IRIBHN, Universite Libre de Bruxelles, Bruxelles, Belgium.
SOURCE: Nature Medicine, (Jun 2006) Vol. 12, No. 6, pp. 671-676.
Refs: 32
ISSN: 1078-8956; E-ISSN: 1546-170X CODEN: NAMEFI
PUBLISHER IDENT.: N1421
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 4 Jul 2006
Last Updated on STN: 4 Jul 2006

AB Hepatic fibrosis, the common response associated with chronic liver diseases, ultimately leads to cirrhosis, a major public health problem worldwide. We recently showed that activation of hepatic cannabinoid CB2 receptors limits progression of experimental liver fibrosis. We also found that during the

course of chronic hepatitis C, daily cannabis use is an independent predictor of fibrosis progression. Overall, these results suggest that endocannabinoids may drive both CB2-mediated antifibrogenic effects and CB2-independent profibrogenic effects. Here we investigated whether activation of cannabinoid CB1 receptors (encoded by Cnr1) promotes progression of fibrosis. CB1 receptors were highly induced in human cirrhotic samples and in liver fibrogenic cells. Treatment with the CB1 receptor antagonist SR141716A decreased the wound-healing response to acute liver injury and inhibited progression of fibrosis in three models of chronic liver injury. We saw similar changes in Cnr1-/- mice as compared to wild-type mice. Genetic or pharmacological inactivation of CB1 receptors decreased fibrogenesis by lowering hepatic transforming growth factor (TGF)-B1 and reducing accumulation of fibrogenic cells in the liver after apoptosis and growth inhibition of hepatic myofibroblasts. In conclusion, our study shows that CB1 receptor antagonists hold promise for the treatment of liver fibrosis. .COPYRGT. 2006 Nature Publishing Group.

SEARCH HISTORY

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     (FILE 'HOME' ENTERED AT 14:57:22 ON 01 JUL 2011)

     FILE 'HCAPLUS' ENTERED AT 14:59:29 ON 01 JUL 2011
                E LOTERSZTAJN SOPHIE/AU
L1           76 SEA ABB=ON  ("LOTERSZTAJIN SOPHIE"/AU OR "LOTERSZTAJN S"/AU OR
                "LOTERSZTAJN SOPHIE"/AU)
                E MALLAT ARIANE/AU
L2           54 SEA ABB=ON  ("MALLAT ARIANE"/AU OR "MALLAT ARIANNE"/AU)
                E GRENARD PASCALE/AU
L3           14 SEA ABB=ON  ("GRENARD P"/AU OR "GRENARD PASCALE"/AU OR
                "GRENARD PASCALE MARIE"/AU)
L4            8 SEA ABB=ON  L1 AND L2 AND L3
L5            0 SEA ABB=ON  L4 AND CBI
L6            7 SEA ABB=ON  L4 AND ?HEPATIC?
L7            4 SEA ABB=ON  L6 AND CB1
                SELECT RN L7 1-4

     FILE 'REGISTRY' ENTERED AT 15:00:54 ON 01 JUL 2011
L8           20 SEA ABB=ON  (169592-56-7/BI OR 1972-08-3/BI OR 329900-75-6/BI
                OR 123653-11-2/BI OR 150314-39-9/BI OR 158681-13-1/BI OR
                168273-06-1/BI OR 192703-06-3/BI OR 51-35-4/BI OR 53847-30-6/BI
                 OR 7782-44-7/BI OR 864169-03-9/BI OR 864169-06-2/BI OR
                864169-08-4/BI OR 864169-10-8/BI OR 864169-12-0/BI OR 864169-16
                -4/BI OR 864169-17-5/BI OR 864199-39-3/BI OR 864199-40-6/BI)

     FILE 'HCAPLUS' ENTERED AT 15:00:58 ON 01 JUL 2011
L9            4 SEA ABB=ON  L7 AND L8

     FILE 'REGISTRY' ENTERED AT 15:02:54 ON 01 JUL 2011
L10           2 SEA ABB=ON  (168273-06-1 OR 288104-79-0)

     FILE 'HCAPLUS' ENTERED AT 15:04:21 ON 01 JUL 2011
L11         983 SEA ABB=ON  L10
L12           8 SEA ABB=ON  L11 AND ((?HEPATIC? OR ?LIVER?)(4A)?FIBROSIS? OR
                HEPATIC FIBROSIS)

     FILE 'MEDLINE, BIOSIS, EMBASE, DRUGU' ENTERED AT 15:05:57 ON 01 JUL 2011
L13          73 SEA ABB=ON  L12

     FILE 'HCAPLUS, BIOSIS, EMBASE' ENTERED AT 15:06:21 ON 01 JUL 2011
L14          73 DUP REMOV L12 L13 (8 DUPLICATES REMOVED)
L15           1 SEA ABB=ON  L14 AND (PRD<20040404 OR PD<20040404)
L16          73 SEA ABB=ON  L14 OR L15
L17          30 SEA ABB=ON  L16 AND CB1
                SAV L16 BOR736L16/A

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     FILE HCAPLUS

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FILE COVERS 1907 - 1 Jul 2011 VOL 155 ISS 2
FILE LAST UPDATED: 30 Jun 2011 (20110630/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Apr 2011
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Apr 2011

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This file contains CAS Registry Numbers for easy and accurate substance identification.

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 30 JUN 2011 HIGHEST RN 1311030-93-9
DICTIONARY FILE UPDATES: 30 JUN 2011 HIGHEST RN 1311030-93-9

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FILE MEDLINE
FILE LAST UPDATED: 30 Jun 2011 (20110630/UP). FILE COVERS 1946 TO DATE.

MEDLINE and LMEDLINE have been updated with the 2011 Medical Subject Headings (MeSH) vocabulary and tree numbers from the U.S. National Libra of Medicine (NLM). Additional information is available at:

http://www.nlm.nih.gov/pubs/techbull/nd10/nd10_medline_data_changes_2011.

The 2011 Medline reload was completed on January 22, 2011.
See HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

See HELP RANGE before carrying out any RANGE search.

FILE BIOSIS
FILE COVERS 1926 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1926 TO DATE.

RECORDS LAST ADDED: 29 June 2011 (20110629/ED)

BIOSIS has been augmented with 1.8 million archival records from 1926
through 1968. These records have been re-indexed to match current
BIOSIS indexing.

FILE EMBASE
FILE COVERAGE: EMBASE-originated material 1947 to 1 Jul 2011 (20110701/ED
Unique MEDLINE content 1948 to present

EMBASE is now updated daily. SDI frequency remains weekly (default)
and biweekly.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

For further assistance, please contact your local helpdesk.

FILE DRUGU
FILE LAST UPDATED: 24 JUN 2011 <20110624/UP>
>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<
>>> THESAURUS AVAILABLE IN /CT <<<